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ARCHIVES of INTERNAL MEDICINE

VOLUME 60 JULY 1937 NUMBER 1

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DIAGNOSIS OF CONGENITAL CYSTIC DISEASE OF THE LUNG

SAMUEL GEORGE SCHENCK, M.D.

BROOKLYN

During the past few years the condition described as congenital cystic disease of the lung has attracted considerable attention. No longer accidentally observed at necropsy, the lesion is recognized during life, and in a number of cases it can be successfully treated. Synonymous terms, such a fetal bronchiectasis, congenital bronchiectasis, atelectatic bronchiectasis and congenital pulmonary lymphangiectasis, have been replaced by the more proper designation, namely, congenital cystic disease of the lung.

Responsible for initiating the recent interest in this condition was Koontz,[1] who reviewed the literature in 1925 and collected reports of 108 proved cases. In a recent communication (1936) I [2] reported from the world's literature an additional 124 cases and 4 original cases, making a total of 236 cases of congenital cystic disease of the lung on record. Since the writing of my last paper, or in the past year and a half, 140 additional reports of cases have been collected. Including the 5 new cases to be described, the grand total is brought up to 381 cases noted since Bartholinus [3] recorded the first case in 1687.

Regarding the lung as a frequent seat of congenital anomalies, Sauerbruch [4] said he believed that cystic disease is not a rare clinical entity, though it is little appreciated by pediatricians. Having treated many patients by surgical removal of the cystic lesion, he was of the opinion that in over 80 per cent of the cases bronchiectasis in children limited to one lobe is of congenital origin. In the fifty-eight lobes which he resected he found no evidence of inflammatory pulmonary changes

From the Department of Radiology, the Jewish Hospital.

1. Koontz, A. R.: Congenital Cysts of the Lung, Bull. Johns Hopkins Hosp. **37**:340-361, 1925.

2. Schenck, S. G.: Congenital Cystic Disease of the Lungs, Am. J. Roentgenol. **35**:604-629 (May) 1936.

3. Bartholinus, T., in Malpighi, M.: Opera omnia, London, R. Littlebury, 1687, pp. 349-350.

4. Sauerbruch, F.: Die operative Behandlung der kongenitalen Bronchiektasen, Arch. f. klin. Chir. **180**:312-320, 1934.

or pleural adhesions, the alterations consisting of cystic bronchial disease and thickening of the pulmonary tissue. Another point of evidence is the absence of a history of colds, influenza and pneumonia.

CLASSIFICATION

Congenital cystic disease of the lung is a developmental malformation which may involve any portion of the bronchial tree or interstitial pulmonary tissue, forming single or multiple discrete cells or pouches. The cysts may be so numerous and small as to give the lobe or lung a honeycomb appearance, or there may be only a solitary sac, which may occupy the entire hemithorax and may even encroach on the heart and mediastinal structures.

Cysts are solitary or multiple (table 1) and contain a milky or turbid fluid at birth. Their fluid contents persist, provided they do not rupture into a neighboring bronchus or bronchiole. If rupture ensues,

TABLE 1.—*Modification of the Anspach and Wolman* Classification of Congenital Pulmonary Cysts*

A. Solitary fluid cyst (at birth)			
1. With no bronchial communication	→	Solitary fluid cyst	
2. With bronchial communication	→	Solitary air cyst	
		a. With free opening	→ Nonexpansile air cyst
		b. With one way mechanism at orifice	→ Expansile air cyst
B. Multiple fluid cysts (at birth)			
1. With no bronchial communication	→	Multiple fluid cysts	
2. With bronchial communication	→	Multiple or trabeculated air cysts	
		a. With free opening	→ Nonexpansile or trabeculated air cysts
		b. With one way valve mechanism at orifice	→ Expansile or trabeculated air cysts

* This classification has been explained by Anspach and Wolman in detail (Surg., Gynec. & Obst. **56**: 635-645, 1933).

air replaces the fluid, and the lesion is designated as a solitary air cyst or as multiple or trabeculated air cysts, as the case may be. If the communicating channel between the cystic cavity and the bronchus is patent during inspiration and expiration, allowing the free passage of air in both directions, the cyst remains stationary in size or nonexpansile. However, should the air become trapped within the cystic space, owing to a valvelike action at the orifice, so that the air enters the cyst but its outflow is obstructed during expiration, the cyst "balloons" out, or becomes expansile. The same mechanism obtains with multiple or trabeculated cysts.

In the 374 cases in which mention was made of the type of cyst found, there were 141 solitary, or single, cysts, the remaining 233 being multiple (table 2). The right lung alone was involved in 157 cases (42

per cent) and the left in 136 (37 per cent); in 78 (21 per cent) the lesion was bilateral.

PATHOLOGIC PICTURE

The precise pathogenesis of cystic disease of the lung is unknown, though the opinion prevails that the lesion is a congenital anomaly or malformation caused by a pinching off of a small pulmonary bud, which continues to develop into pulmonary tissue. The retained secretions, apparently of mucosal origin, having no bronchial outlet, distend the enclosed space, which encroaches on and compresses the surrounding alveoli. The wall of the cyst is usually made up of high or low columnar epithelium, with or without cilia, muscle and elastic tissue, and cartilage, sporadically arranged, a picture which points to a bronchial origin. The absence of anthracotic pigment within and in the vicinity of the wall of the cyst indicates the functionless nature of the tissue and its congenital origin.

TABLE 2.—*Incidence of the Types of Cysts*

	Infants and Children	Adults	Total
Solitary Cysts			
Fluid cyst	28	21	49
Air (nonexpansile) cyst	22	33	55
Balloon (expansile) cyst	32	5	37
Total number of cases of solitary cysts	82	59	141
Multiple Cysts			
Fluid cysts	25	13	38
Air (nonexpansile) cysts	50	138	188
Balloon (expansile) cysts	5	2	7
Total number of cases of multiple cysts	80	153	233

In 45 cases in which necropsy was performed, other congenital abnormalities were noted besides the cystic malformation of the lung. The most frequent anomaly was some pulmonary defect, as an accessory lobe or lung, which not infrequently harbored the cystic defect.

SYMPTOMS

The diagnosis is dependent chiefly on the roentgenographic findings, aided by a painstaking study of the history. With symptoms present since birth or shortly thereafter, in the absence of a history of severe disease of the respiratory tract, and with the roentgenographic evidence of a gross pulmonary pathologic condition of the type to be described, the diagnosis of the congenital lesion is in most cases not difficult. The more prominent symptoms (table 3), especially in infants and children, are recurring attacks of dyspnea and cyanosis,[5] with or without cough.

5. Morgan, E. A., and Brown, A.: Cyanosis of the New-Born, J. A. M. A. **105**:1085-1088 (Oct. 5) 1935. It is of interest to note that Morgan and Brown failed to mention congenital cystic disease of the lung in their classification of the causes of cyanosis of the new-born.

These attacks may be so mild as to be overlooked or may assume such serious proportions as to cause fear of terminating fatally. Dyspnea and cyanosis are most prominent in the expansile air cysts and may not be relieved until the cyst is punctured and the trapped air withdrawn or until the cyst is deflated by rupture into the pleural space, resulting in a partial pneumothorax, or is emptied when the valvelike obstruction at its bronchial orifice is removed.

Expectoration is dependent on the presence of a channel between the cyst and the bronchus. With such a communication the cystic contents are often infected, and the symptoms are not unlike bronchiectasis from contractive causes. The elevation in temperature, which is seldom great, is dependent on the presence or absence of infection. Another important symptom which is by no means uncommon is

TABLE 3.—*Frequency of the More Common Symptoms*

	Infants and Children	Adults	Total
Cough	76	141	217
Dyspnea	76	78	154
Expectoration	40	112	152
Cyanosis	52	23	75
Fever	28	44	72
Hemoptysis	5	47	52
Malnutrition	29	21	50
Thoracic pain	6	33	39
Weakness	10	23	33
Anorexia	14	6	20
Wheezing	11	8	19
Vomiting	16	1	17
Palpitation	1	11	12
Epigastric distress	..	7	7

hemoptysis, which may be slight and may result in the expectoration of blood-streaked sputum or of frank blood. Many of these patients have been needlessly treated for tuberculosis because of the bloody expectoration and the roentgenographic finding of a cavity in the upper lobe of a lung, notwithstanding the sputum has persistently failed to show tubercle bacilli. Pains in the chest may or may not be present. Among the less frequent symptoms may be mentioned weakness, anorexia, palpitation and vomiting, particularly in children. Occasionally the distress from an intrathoracic lesion is referred to the epigastrium. This referred pain may mislead the clinician at first, and this possibility must be borne in mind. The symptoms of dyspnea and cough, sometimes with pronounced wheezing, present in 19 cases in this series, may suggest a diagnosis of asthma and for a time may overshadow the underlying pathologic condition.

The physical signs are seldom definite but not infrequently indicate the presence of a pulmonary lesion. The signs naturally vary with the size and number of cysts and the nature of their contents (air or

fluid). Other congenital malformations are sometimes present. In a number of cases the cystic lesion in the lung is a purely accidental finding, no symptom or signs being presented. The discovery may be at birth or soon thereafter, or the lesion may escape detection until death occurs as a result of other causes and is revealed at necropsy (table 4). Not infrequently (18 cases) the condition is accidentally found during a roentgenographic examination for some other malady.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis frequently rests on a painstaking roentgenologic examination, which includes anteroposterior and lateral views as well as a careful roentgenoscopic study. In rare instances stereoscopic films are necessary in order to furnish additional information.

Not infrequently the roentgenograms portray extensive pathologic changes in a patient who appears comfortable and presents surprisingly few symptoms. It is well to remember this point in arriving at a diagnosis of congenital pulmonary malformation.

TABLE 4.—*Age at Which Condition Was Recognized*

	Number of Cases
At birth	36
Under 1 yr	57
Between 1 and 15 yr	68
Over 15 yr	207
Total	368

A solitary fluid cyst is observed in the roentgenograms as a moderately dense, opaque, globular shadow which lies within the pulmonary parenchyma. The density of the cystic shadow is slightly less than the opacity cast by the heart and often can be separated from the cardiac shadow in the lateral studies. If there is an uncomplicated fluid cyst the aspirated specimen resembles amniotic fluid, appearing slightly milky or albuminous and moderately viscid. Cultures show no growth; the microscopic study may reveal the presence of ciliated columnar epithelium and, occasionally, goblet cells. The lesion must be differentiated from a solid tumor, acquired cystic disease and an inflammatory lesion.

Among the solid tumors, malignant growth, teratoma, chondroma and ganglioneuroma may be mentioned. Malignant disease is readily excluded by the history, physical examination and clinical course in each case. A teratoma should offer little difficulty, because it originates in the mediastinal spaces and usually begins to develop after puberty. Ganglioneuroma and chondroma may be more difficult to identify at first. The fact that a solid tumor is more opaque roentgenographically and its outer border more sharply defined than the walls of a cyst, which has

rather poorly defined borders as compared with those of a tumor, will tend to differentiate the two conditions. Furthermore, a tumor has the tendency to grow, whereas a fluid cyst remains stationary for a long period. Lastly, if doubt still exists, puncture of the cyst and the obtaining of the characteristic fluid will decidedly exclude the presence of a solid tumor.

In acquired cystic disease the lesions that may simulate a congenital solitary fluid cyst are echinococcic, dermoid, hydatid and mediastinal cysts. An echinococcic cyst is excluded by the complement fixation test and by the presence of eosinophilia. Urticaria is not infrequently present and other lesions may be found. When the cyst ruptures into a bronchus, the characteristic hooklets in the sputum establish the diagnosis. A dermoid cyst is differentiated by the presence of bone or teeth in the roentgenograms or by the finding of hair or cartilage in the expectoration. Hydatid and mediastinal cysts are mediastinal in origin and usually produce little or no dyspnea. If rupture of a hydatid cyst occurs, the watery nature of the fluid is rather characteristic, and hooklets and fragments of membrane may be found in the sputum.

Inflammatory lesions are among the more common conditions that must be separated from a congenital solitary fluid cyst, and included among these acquired processes are pneumonia, localized fluid or encapsulated empyema, pulmonary abscess and an interlobar collection of fluid or pus. Pneumonia should offer no difficulty. When there is encapsulated fluid, the opacity is outside the lung, and the history of a recent infection is elicited. Furthermore, the patient appears acutely ill, and the temperature is "spiked," whereas the patient with cystic disease is often relatively comfortable. The history and the appearance of the patient may similarly exclude a diagnosis of interlobar fluid. The fluid usually appears on the roentgenogram as a wedge-shaped opacity taking the direction of the interlobar fissure. In separating pulmonary abscess from cystic disease the previous history and clinical course, the inconstant roentgenographic findings and the poorly defined borders, due to the surrounding pneumonitis, present in pulmonary suppuration tend to furnish little difficulty. Thoracentesis, with examination of the aspirated fluid, may be necessary to establish the diagnosis.

A solitary nonexpansile air cyst reveals a pocket of air that is intrapulmonary and usually globular or spherical. A moderately thin capsule or wall delimits the air space, which shows no pulmonary markings but may reveal fine linear strands traversing the cystic space in a slightly curving fashion indicative of trabeculations. Roentgenoscopically an increase in illumination within the cyst is often observed during forceful inspiration. This type of cyst must be separated from an emphysematous bulla, which shows no delimiting wall, from localized or partial pneumothorax and from a tuberculous cavity. In addition to

the fact that no wall surrounds the air pocket which lies outside of pulmonary parenchyma, localized pneumothorax appears irregular in contour and does not persist unchanged for a long period. On deep inspiration no increased illumination within the cystic space is noted roentgenoscopically. A tuberculous vomica may resemble a solitary air cyst, especially a cyst that is located in the upper lobe. However, the dense, broader walls and the concomitant pulmonary infiltration and changes observed in tuberculosis are absent in cystic disease. The fact that patients with cystic disease have been treated for tuberculosis indicates the necessity for the examiner to be cyst conscious if a proper separation of the two conditions is to be made.

In the expansile or balloon type of cyst, with increasing symptoms of dyspnea and cyanosis, the roentgenographic picture is rather unusual. There is an obliteration of the pulmonary markings, with air filling the entire hemithorax from apex to base. The findings are not unlike those of complete pneumothorax, from which it may not be so readily differentiated. The heart and mediastinal contents appear displaced to the normal side, and the diaphragmatic leaf on the affected side is depressed and flattened. A slight haziness is often noted in the apex, and the costophrenic angle is obliterated. These findings represent atelectatic pulmonary tissue due to the compression of the lung in all directions by the expanding cyst. Instead of the collapsed lung appearing as a broad stump at the root, as observed in cases of pneumothorax, the hilar shadow is narrow and elongated, owing to the fact that the expansile cyst is compressing the pulmonary tissue peripherally. The cystic wall can usually be detected, especially its mesial portion, overlapping part of the heart and encroaching on the mediastinum. The fine, slightly curved strands traversing the cystic space are often portrayed. In infants and children the affected side of the chest bulges and lags on respiration. Thoracentesis releases air under pressure. When there is an air cyst, the walls of which lack clarity or merge with the thoracic wall and are thus obscured, induced pneumothorax results in unusually clear roentgenograms which portray the cystic space lying within the partially collapsed lung. The air, artificially introduced into the pleural space, retracts the outer border of the lung and the cystic wall from the ribs. The contrast between the air in the pleural cavity and that in the cystic space with its surrounding capsule lying in the partially retracted lung establishes the diagnosis and differentiates a cystic condition from pneumothorax, either acquired or congenital.

Multiple air cysts (polycystic lung) are characterized by their sharply defined spherical cavities, discrete and irregularly arranged, and the lack of pulmonary infiltration between them. In these cases there is a paucity of clinical symptoms, unlike cases of acquired bronchiectasis, with which the condition may be confused. In the sacculated form of

bronchiectasis from contractive processes, the cavities are smaller, less discrete and more or less definitely arranged in relation to the affected bronchus or bronchi. In addition, there is roentgenographic evidence of secondary pulmonary changes around and between the cavities. Bronchiectasis often follows a severe respiratory infection, whereas the absence of such a history and the presence of more or less mild symptoms since birth or early childhood indicate the probability of an underlying congenital malformation. However, in some instances differentiation is impossible, and an absolute diagnosis must be deferred until necropsy reveals the absence of pigmentation in the walls of the cavities which would indicate their congenital origin.

When there are multiple air cysts, diaphragmatic hernia or eventration can readily be excluded by the absence of gurgling sounds on auscultation of the chest and by the intake of a barium meal.

TABLE 5—*Causes of Death*

	Infants and Children		Adults		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Congenital cystic disease	70	60.9	44	56.4	114	59.0
Pneumonia	26	22.6	7	9.0	33	17.0
Tuberculosis	2	1.7	3	3.8	5	2.7
Cardiac failure	2	1.7	3	3.8	5	2.7
Other causes	15	13.1	21	27.0	36	18.6
Total	115		78		193	

Occasionally, bronchoscopic examination and visualization of the bronchial tree with iodized poppy-seed oil 40 per cent may aid in the diagnosis. Although the presence of pus in the bronchus may not differentiate bronchiectasis from an infected cyst, nevertheless, the increased clarity of the cavity filled with iodized oil affords a better opportunity to separate the two conditions. When there is a fluid cyst with no bronchial connection, the opaque oil will fill the entire bronchial tree except for the region occupied by the fluid cyst. When there is a large air cyst, iodized oil may be introduced by thoracentesis under roentgenoscopic control. This procedure is feasible when the outer wall of the cyst lies in close approximation with the thoracic wall.

The visualization of the oil-filled cystic space aids materially in rendering a correct diagnosis.

PROGNOSIS AND TREATMENT

The prognosis and treatment of this congenital defect depend on the number, size, type and location of the cystic lesions, as well as on the age of the patient and the presence or absence of infection. Although the condition is not incompatible with long life, nevertheless the mortality is high among infants and children, especially those with the expansile type of cyst (table 5). Surgical extirpation of the cystic

defect or lobectomy is the only rational form of treatment in selected cases. Sauerbruch,[4] who performed fifty-eight lobectomies for congenital bronchiectasis, including two extirpations of the whole lung accomplished in two or more stages, with six deaths and fifty-one complete cures without a fistula, stated his conviction that the treatment of choice for a congenital malformation is extirpation of the involved lobe. This operation should be performed early, before the secondary alterations have time to develop. Edwards and Thomas,[6] Flemming-Møller,[7] Sultan,[8] Eloesser,[9] Harrington,[10] Melchior [11] and others also have performed successful lobectomies on children as well as on adults.

Although the procedure is attended with grave dangers, the reduction in the mortality and morbidity in these operations offers hope and encouragement to these unfortunate patients.

REPORT OF CASES

The following reports of new cases are added to the 4 which I [2] have already published elsewhere:

CASE 1.—R. E., a full term infant, weighing 8 pounds and 10 ounces (4,000 Gm.), was delivered by low forceps with no apparent injury. She was discharged from the hospital with her mother in twelve days in good condition, with no record of convulsions, cyanosis or snuffles. Shortly afterward the mother noticed that the infant "snorted" and made peculiar sounds when nursing. There were also several short "spells of heavy breathing." When 2 months old the infant had a mucopurulent nasal discharge, for which a physician prescribed nose drops. Immediately after their use, the child began to cough and gag. Although the drops were discontinued, the bouts of coughing and gagging, with occasional vomiting, persisted. There was a rise of temperature to 102 F. for several days. The physician remarked that the child "looked like a thymus baby." The symptoms persisted for three weeks with more or less severity until the night prior to the infant's admission to the hospital, when she suddenly became markedly dyspneic and cyanotic, with a harassing unproductive cough.

When brought to the hospital, the infant appeared in a moribund condition. Cyanosis was pronounced, and she gasped for breath, utilizing all the accessory respiratory muscles. The eyes were staring, and the body was limp. She appeared to be a well nourished and well developed infant of 3 months. The

6. Edwards, A. T., and Thomas, C. P.: One-Stage Lobectomy for Bronchiectasis: An Account of Forty-Eight Cases, Brit. J. Surg. **22**:310-331, 1934.

7. Flemming-Møller, P.: Congenital Thoracic Cysts and Lung Deformities in the Roentgen Picture, Acta radiol. **9**:460-473, 1928.

8. Sultan, G.: Bronchuscyste, Zentralbl. f. Chir. **52**:869-873, 1925.

9. Eloesser, L.: Congenital Cystic Disease of the Lung, S. Clin. North America **8**:1361-1373, 1928; Surg., Gynec. & Obst. **52**:747-758, 1931; Radiology **17**:912-929, 1931.

10. Harrington, S. W.: Surgical Treatment of Intrathoracic Tumors, Arch. Surg. **19**:1679-1725 (Dec.) 1929.

11. Melchior, E.: Zur Kenntnis der kongenitalen tracheobronchialen Cysten der Lunge, Zentralbl. f. Chir. **56**:2626-2630, 1929.

anterior fontanel was opened but showed no bulging. The pupils were dilated and reacted poorly to light. The nose revealed a slight mucopurulent discharge, with evidence of mild congestion of the nasal and pharyngeal mucosa. The heart rate was rapid, and the sounds and rhythm were normal. The right lung was hyperresonant on percussion, and the breath sounds appeared distant or absent. Posteriorly, along the vertebral border, some fine râles and some bronchial breathing were heard. The left lung was normal except for a few scattered râles. No abnormal findings were observed on examination of the abdomen.

When admitted to the hospital the infant had a temperature of 101 F. The blood count showed 31,000 white blood cells. Roentgenographic examination (fig. 1) revealed multiple large and small cystic areas that occupied the entire right side of the thorax, encroaching on the heart and mediastinal spaces, which

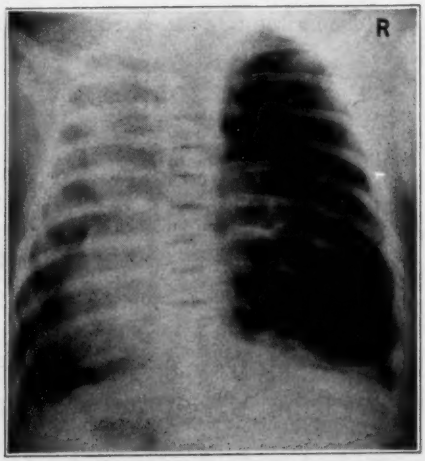

Fig. 1 (case 1).—The right lung shows many large and small air cysts, the expansile nature of which is recognized by the displacement of the heart and mediastinal contents to the opposite side and the encroachment of the cystic spaces on the mediastinum and the left lung.

were decidedly shifted to the left. The cystic spaces contained air and presented thin but well formed walls. The lung was apparently crowded out in all directions, appearing compressed in the apex and at the base, especially in the costophrenic sinus. The upper border of the opacity at the costophrenic sinus and the right diaphragmatic cusp were concave, conforming to the pressure effect from the contiguous cysts. The borders of a large cyst were discernible overlying the mediastinum and the heart and encroaching considerably on the left lung. The roentgenographic findings were interpreted as indicating congenital multiple or trabeculated expansile cysts of the lung.

The infant was placed in an oxygen tank, and 100 cc. of 5 per cent solution of dextrose was given intravenously. A needle was inserted into the right side of the chest posteriorly, and 30 cc. of air was withdrawn under pressure. Following this procedure there was temporary relief from the dyspnea and cyanosis,

which returned to an alarming degree the same afternoon, accompanied with a rise in temperature to 106 F. Death occurred within twenty-four hours after the infant's admission to the hospital.

Gross Postmortem Examination.—Only the lungs were obtained. What was considered to be the right lung (fig. 2) consisted of a portion of tissue measuring 10.5 by 8 by 2.5 cm. The external surface was smooth and shiny, except over an area measuring 4 by 3 cm., where it appeared slightly roughened. The cut surfaces were entirely composed of cavities varying from 0.2 to 6 cm. in diameter separated by delicate partitions. Some of the cavities communicated with each

Fig. 2 (case 1).—Gross specimen of the right cystic lung, showing cavities of various sizes and practically no normal pulmonary tissue.

other by narrow openings. The internal surface of the cavities was glistening, dotted in places with red areas or traversed by delicate blood vessels. Accompanying this was a small portion of tissue from the left lung. Two sections from the left lung and one from the cystic structure were taken for microscopic study.

Microscopic Postmortem Examination.—A preparation from the intact lung showed good-sized air spaces containing some cellular débris and occasional large mononuclear cells. Some of the air spaces were large. All the blood vessels appeared markedly distended with blood. The lining cells of the bronchi and bronchioles were well preserved. Another preparation from the same lung presented a similar structure. No cellular infiltration was noted.

A preparation from the left lung (figs. 3 and 4) showed broad bands of vascular hyalinizing fibrous connective tissue and broad bands of a rather loose fibrous connective tissue. On both surfaces of these bands were mounted low cuboidal and cylindric cells. In places the surface was thrown into broad folds covered with cuboidal cells. Occasional bundles of smooth muscle and some lumens resembling acini of mucous or serous glands were noted beneath the epithelium-covered surfaces. In one place there was a strand of large mononuclear cells with golden yellow granular cytoplasm and nearby a few eosinophilic leukocytes. The capillaries

Fig. 3 (case 1).—Photomicrograph showing multiple cystic spaces lined with low cuboidal and cylindric epithelium, thrown into folds which contain occasional bundles of smooth muscle and some lumens resembling acini of mucous or serous glands; × 40.

were distended with blood. Freshly extravasated blood was noted in some areas. Masses of granules staining blue and lavender were seen in the centers of some of the larger bands of connective tissue. Around some there were aggregations of cells and cell nuclei. In others the granular material lay free in the connective tissue, with no surrounding cellular reaction.

Staining revealed many areas of elastic tissue situated in the broad bands beneath the epithelial surfaces.

Comment.—The right lung was apparently entirely replaced by many small and large cystic spaces with thin walls composed of cuboidal or cylindric nonciliated epithelium, loose fibrous tissue, occasional bundles of smooth muscle, mucous or serous glands and elastic fibers, indicating a bronchiogenic origin. There was no evidence of pneumomia in either lung. The clinical course and the roentgenographic findings, together with the postmortem observations, clearly demonstrated that this was a case of multiple congenital pulmonary cysts, one or more of which were

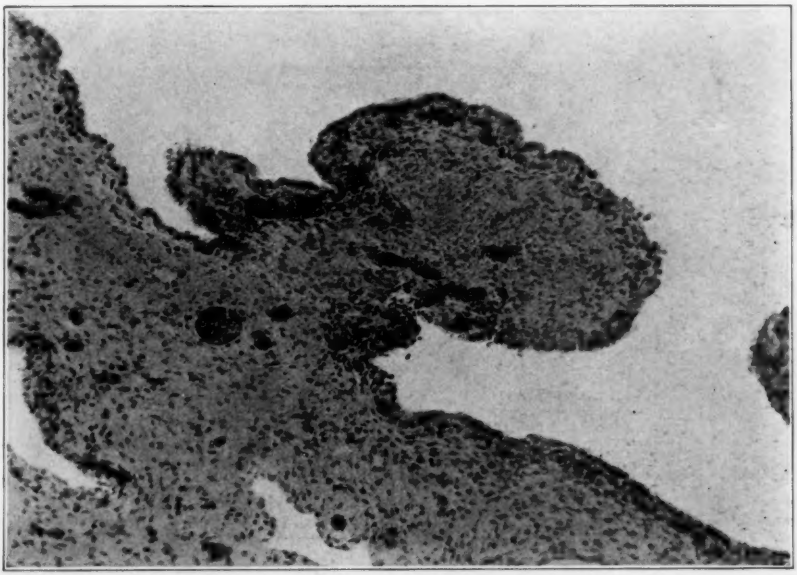

Fig. 4 (case 1).—Photomicrograph showing details of a portion of the wall of one of the cystic formations; × 200.

of the expansile type, which accounted for the alarming symptoms of dyspnea and cyanosis resulting in sudden death.

Case 2.—N. F., a man aged 45 years, a shoemaker, came to the outpatient department with a history of pulmonary complaints for two years. The only symptom referable to the chest was a slight cough. Although his appetite was good, he believed that he had lost some weight. There were no sweats, elevation in temperature or weakness. Two years previously he was told that his lungs were affected. During this time he was at two institutions, where he was regarded as having tuberculosis, notwithstanding persistently negative results of examination of the sputum. This opinion was based on the roentgenographic examination, which showed what was interpreted as persistent pneumothorax at the base of each lung.

On physical examination the patient appeared well developed, well nourished and comfortable. There were diminished breath sounds at the base of both lungs, with sibilant and sonorous râles on both sides. The chest appeared emphysematous. Aside from the presence of atrophic rhinitis, the findings on examination were irrelevant.

Roentgenographic study (fig. 5) revealed a large spherical area of transparency in the lower third of each lung extending to the diaphragm. A thin curvilinear shadow was observed superiorly, demarcating the air space from the normal lung. In the lateral view the cystic wall could be readily visualized. A dense opacity cast by compression of the lung obliterated the extreme costophrenic sulcus on each side. After the instillation of iodized oil into the bronchial tree (fig. 6) the cystic spaces did not fill. The bronchial branches were displaced

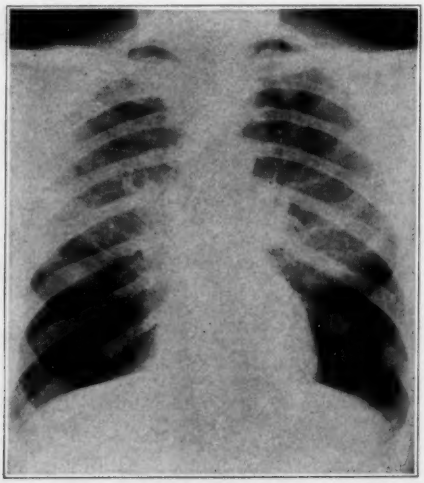

Fig. 5 (case 2).—A large cystic space occupies the lower part of both lungs. The upper border of the cyst in each instance appears as a thin curvilinear shadow.

around the cyst and showed bronchiectatic changes. The roentgenographic impression was bilateral air cysts which probably communicated with a neighboring bronchus by a tortuous or imperfect channel, so that the iodized oil could not find its way into the cyst.

The Wassermann and Kahn tests showed a 4 plus reaction. A urologic survey revealed hypertrophy of the median lobe of the prostate. Neurologic and dermatologic examinations revealed no abnormality.

The patient was diligently observed for six years, during which time he received antisyphilitic treatment and roentgenologic studies were made. The physical signs and roentgenographic appearance of the lungs remained unchanged. At present there are no symptoms or complaints. The Wassermann and Kahn tests are negative. Yet the roentgenographic appearance of the lungs remains the same as at the first study made six years ago.

Comment.—The presence of syphilis in no way alters the fact that this is a case of congenital pulmonary cystic disease. Syphilis has been considered by some observers as the underlying etiologic factor in this condition. However, negative results of serologic tests are most frequently encountered in patients with this pulmonary anomaly, and a complete autopsy usually reveals no stigmas of syphilitic infection. Hence the presence of syphilis is considered to be a coincidental rather than an etiologic finding.

The roentgenographic signs, unchanged for six years, lead to only one logical conclusion; namely, this is a case of congenital cystic disease

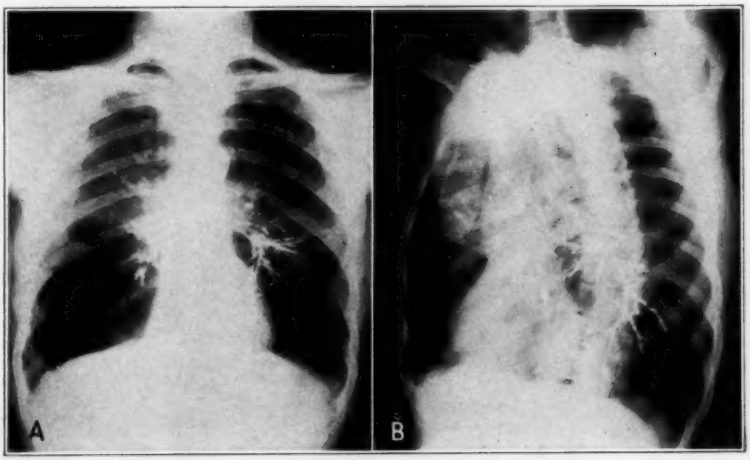

Fig. 6 (case 2).—*A*, the bronchographic medium failed to find its way through the tortuous, imperfect channel between the bronchus and the cystic cavity. The iodized oil visualizes the blunted bronchial branches, which end blindly. *B*, the oblique view shows the displacement of the bronchial tree by the cystic malformation, the delimiting border of which is more clearly depicted than in the anteroposterior view.

of the lung. Like many others of its kind, this case is a good illustration of minimal clinical symptoms with maximal roentgenographic findings, which are out of proportion to the patient's complaints and physical signs.

Case 3.—F. M., a woman 47 years old, complained of a dry chronic cough and shortness of breath for three years. She was the mother of four children, all living and well. Physical examination showed that she was obese and had a nonproductive hacking cough but was not in acute distress. The pharynx was moderately injected, and the voice was hoarse. Auscultation showed that the heart was normal. The lungs presented normal resonance, with slightly harsh

breath sounds in the right side of the chest. No râles were heard. The remainder of the examination gave unimportant results.

On roentgenographic examination (fig. 7) a well circumscribed ovoid area of opacity was observed in the right side of the chest lying superior to the root. The shadow appeared homogeneous, with sharp borders. The mediastinal spaces showed no encroachment or displacement. The remaining lung bed was clear and the opposite pulmonic field likewise. The roentgenographic findings suggested an intrapulmonary tumefaction or a fluid cyst.

The Wassermann and Kahn tests were negative. Bronchoscopy showed the presence of extrinsic pressure on the trachea and the right main bronchus, the interior of which was normal.

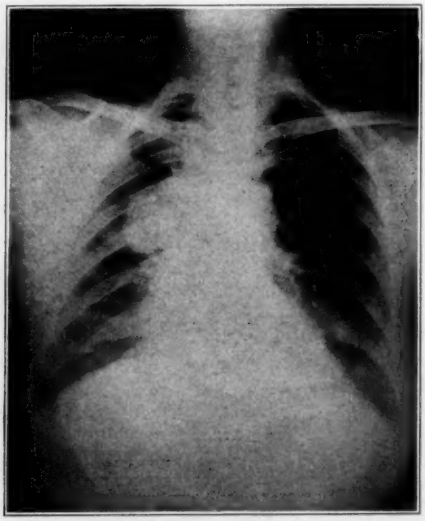

Fig. 7 (case 3).—An ovoid opacity is present in the right lung lying superior to the root and adjacent to the mediastinum. The shadow is intrapulmonary. No mediastinal encroachment is observed. The finding strongly suggests a solitary fluid cyst.

The patient was given several courses of high voltage roentgen treatments, with no effect on the symptoms or on the size and appearance of the opacity.

For over a year the roentgenographic appearance of the globular mass remained unchanged.

Comment.—The roentgenologic diagnosis of a congenital fluid cyst is warranted from the appearance of the shadow, which shows no tendency to grow and which is entirely uninfluenced by intensive roentgenotherapy. Although repeated examinations were made during the course of a year, the roentgenographic findings remained unchanged.

CASE 4.—J. P., a man 29 years old, a baker, entered the outpatient department with the chief complaints of cough and pain in the chest for two years. Except for one sister, 26 years old, who had had pulmonary tuberculosis for three years, the family history was unimportant. At the age of 14 the patient had dry pleurisy, and at 15 he suffered from bronchitis. Two years before admission to the clinic he expectorated blood-tinged sputum over a period of a month. Since then he had been complaining of pains in the anterior portion of the chest and cough, occasionally expectorating white phlegm but no blood. There had been no afternoon fever and no night sweats. He felt strong and had gained about 40 pounds (18 Kg.) in the past two years.

Physically the patient showed no abnormality aside from that in the chest—slight dulness in the apex of the right lung posteriorly and a few crepitant râles at the base of the left lung which disappeared with coughing.

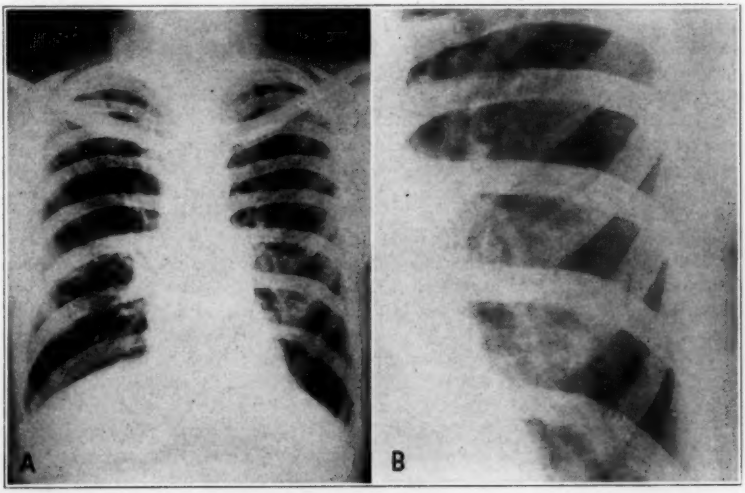

Fig. 8 (case 4).—*A*, a small annular shadow is noted in the left pulmonary bed, slightly below and external to the root. The finding suggests the presence of a small solitary air cyst. *B*, the same portion magnified.

Roentgenographic study (fig. 8) portrayed a small annular, or ring, shadow slightly below the midportion of the left thoracic field near the root. The shadow presented a well defined outer border and suggested the presence of a small solitary air cyst. A tuberculous cavity was not considered likely because of the location in the midthoracic field and the absence of perifocal infiltration. Both apexes were clear, and no roentgenographic evidence of the concomitant infiltration of a tuberculous nature was found.

Passive bronchographic study revealed normal findings bilaterally. The iodized oil had apparently failed to enter the cystic cavity. No bronchiectasis or other abnormality was disclosed.

The patient was observed for more than a year, during which time no change in the roentgenographic findings was noted. Repeated examinations of the sputum revealed no tubercle bacilli.

Comment.—A diagnosis of a tuberculous cavity can well be ruled out by the location of the lesion in the lower half of the pulmonary field, by the sharply defined, thin capsule, by the absence of other changes around the cyst and in the remaining portions of the lung, especially the apex, and by the constancy of the shadow, which remained unchanged in size and shape for a year. The patient's general good health, the uninterrupted gain in weight and the persistently negative results of examinations of the sputum strongly tend to exclude the presence of an ulcerative tuberculous lesion. The well defined membrane surrounding the small air pocket which persisted unchanged over a long period serves to exclude the possibility of an emphysematous bleb or bulla.

CASE 5.[12]—N. W., a woman 58 years old, presented a history of cough and loss of weight (70 pounds [32 Kg.]) of one year's duration. Marked progressive weakness and dyspnea, with transient orthopnea, were additional symptoms. The cough was productive of small amounts of greenish sputum. There were no night sweats or afternoon fever. No previous history of disease of the respiratory tract was elicited.

When admitted to the hospital the patient showed a temperature of 98 F., a pulse rate of 88 and a respiratory rate of 21. The blood pressure was 132 systolic and 64 diastolic. Physical examination showed a poorly nourished, chronically ill woman who coughed frequently. The skin was loose, showing evident loss of weight. The eyes appeared sunken and the disks hazy. The teeth were decayed and the gums infected. The remaining examination revealed no abnormality except in the lungs. The expansion of the left side of the chest appeared greater than that of the right. No changes in the percussion note or breath sounds were noted. D'Espine's sign was not elicited. In the lower half of both pulmonary fields many mixed râles, persisting after coughing, were heard. The clinical impression was advanced bilateral tuberculosis. Repeated examination of the sputum failed to show the presence of the tubercle bacillus.

The roentgenographic examination (fig. 9*A*) revealed considerable striping in the lower half of each pulmonary field, the apexes being relatively clear. There was a suggestion of a lattice-work appearance, with small annular shadows, often observed in bronchiectasis. The right diaphragmatic cusp presented an adhesion at the costophrenic angle. Bronchography (figs. 9*B* and 10) revealed diffuse bilateral bronchiectasis of the saccular or cystic variety.

Comment.—Without a previous history of severe respiratory infection to account for the present findings in the chest, in the absence of tubercle bacilli in the sputum at repeated examinations and with evidence of a diffuse involvement in both lungs, particularly in the lower half, the diagnostic impression of congenital cystic disease, often designated as congenital bronchiectasis and honeycomb lungs, is most plausible.

SUMMARY AND CONCLUSIONS

A total of 381 cases of congenital cystic disease of the lung, including 5 new cases here described, are analyzed, in groups according to the

12. Dr. G. H. Koiransky gave me permission to report this case.

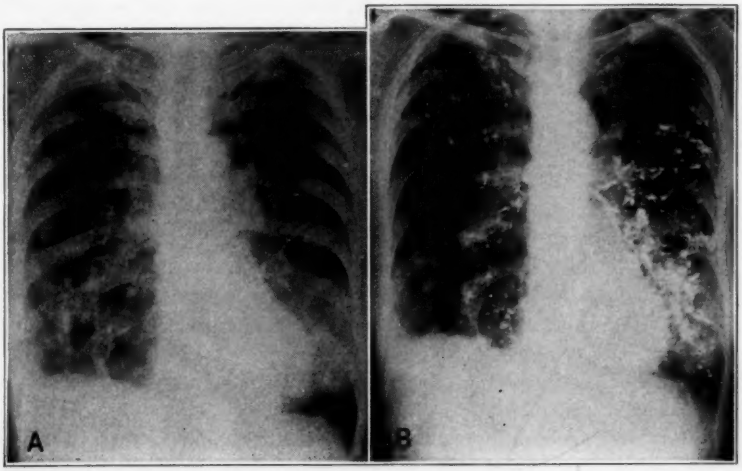

Fig. 9 (case 5).—*A*, the lower half of each lung shows marked striping and many small annular shadows. A diaphragmatic adhesion is present in the right costophrenic sinus. The findings suggest bilateral bronchiectasis, probably of congenital origin. *B*, the polycystic cavities in the left lung are filled with the bronchographic medium. Note the presence of the small cystic areas in the lower portion of the upper lobe as well as in the lower lobe.

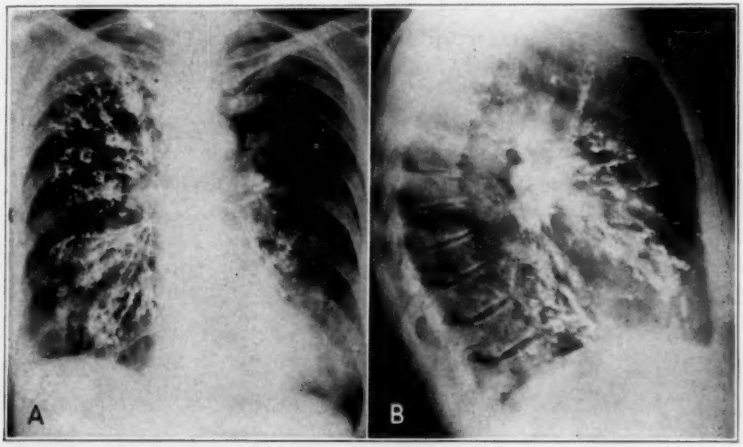

Fig. 10 (case 5).—*A*, bronchographic study of the right lung shows innumerable small cavities throughout the entire pulmonary field. The widespread involvement indicates a polycystic lung. *B*, a lateral view of the chest shows the multiple small air cysts communicating with the bronchi, appearing partially filled with the iodized oil.

ages of the patients, in regard to sex, symptoms, type of cyst, cause of death and other characteristics. From this study the congenital pulmonary malformation is readily recognized by the history and the roentgenographic examination. In most cases the condition is diagnosed by roentgenograms alone. The main difficulty is to differentiate this congenital malformation from acquired cystic lesions, which can usually be accomplished by careful study and observation.

The following points are reiterated for emphasis:

1. Congenital cystic disease of the lung is not a rare pathologic curiosity. Of the 381 cases reported in the literature, over 145 were recorded in the past two years.

2. With mild symptoms of respiratory disturbance dating from birth or early childhood, and in the absence of a history of severe infection of the respiratory tract, a congenital pulmonary malformation should be suspected.

3. The persistently unchanged roentgenographic findings usually indicate a congenital cystic lesion, whereas in acquired conditions follow-up roentgenograms show relatively frequent changes.

4. The lesion is usually attended with grave prognostic dangers in infants and young children who present the large cystic defect of the expansile type.

5. In older patients the malformation may not be incompatible with long life.

6. There are only 5 cases [13] recorded in which the cystic space after emptying its contents collapsed and its wall absorbed and the patient recovered completely, with no visible evidence of the lesion in the roentgenograms.

7. Attacks of dyspnea and cyanosis, especially in infants and children, may be caused by a congenital cyst of the lung. Physicians must be cyst conscious in order to arrive at the correct diagnosis.

8. Pulmonary malformations must be considered among the causes for cyanosis of the new-born.

9. In children bronchiectasis limited to one lobe is usually of congenital origin.

10. Hemoptysis is a not uncommon symptom in congenital cystic disease of the lung. It was a prominent symptom in 52 cases.

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13. Vollmer, H.: Cystische Lungengebilde im Kindesalter, Ztschr. f. Kinderh. **46**:810-817, 1928. Zarfl, M.: Zur Kenntnis der geschwulstförmigen Luftansammlungen (Pneumatocelen) im Brustraum, ibid. **54**:92-102, 1932. Croswell, C. V., and King, J. C.: Congenital Air Cyst of the Lung, J. A. M. A. **101**:832-834 (Sept. 9) 1933. Fleming, G. B.: Five Cases of Congenital Lung Cyst, Arch. Dis. Childhood **9**:201-212, 1934. Schenck, S. G., and Stein, J. L.: Congenital Lung Cysts in Infants and Children, Radiology **24**:420-432, 1935.

11. An annular shadow or cystic space in the upper lobe may indicate a congenital anomaly and not necessarily a tuberculous vomica.

12. The most important observation in the diagnosis of a pulmonary air cyst is the presence of the surrounding wall or delimiting membrane within the pulmonary parenchyma. A cystic wall should be looked for in the roentgenograms.

13. A gross pathologic condition noted roentgenographically, with few or no symptoms or signs, often indicates a congenital malformation, such as a cystic lung.

14. The treatment of choice is surgical, whenever feasible, provided the symptoms warrant such a dangerous procedure and the condition is limited to one lobe. The operation of choice is extirpation of the cyst, if possible, or lobectomy.

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CAUSE OF DEATH IN TULAREMIA

LEE FOSHAY, M.D.
CINCINNATI

In the accumulating literature on clinical studies of tularemia there is expressed a growing belief that tularemic pulmonary complications are of ominous prognostic significance and that tularemic pneumonia is in itself the chief cause of death from this infection. Personal experience and a study of case records covering more than 750 cases of acute tularemia are not in agreement with this view. A survey of the morbidity and mortality data now available indicates that tularemic pneumonia cannot possibly be the chief cause of death.

FATALITY RATE

Up to the close of 1935 there had been reported to the United States Public Health Service 6,206 cases of tularemia, with 299 deaths, a fatality rate for the series of 4.8 per cent. Despite accurate methods for diagnosis, many nonfatal cases and an unknown number of deaths escape detection annually. The typhoidal clinical type is the one most frequently misdiagnosed. Also, as I shall show presently, this type carries a significantly higher mortality rate than the other clinical types. This leads me to believe that tularemic deaths are escaping recognition (and reporting) at a proportionally higher rate than 1:20 against nonfatal cases not reported on. I know at present of 2 such deaths, each from the typhoid type and recorded as due to "lobar pneumonia." This experience is doubtless not unique. Consequently I believe the true fatality rate is higher than the one recorded, and I should estimate this rate as not less than 6 per cent.

INCIDENCE OF TULAREMIC PNEUMONIA

A systematic roentgenologic study of the lesions of pulmonary tularemia is being carried out by Blackford [1] and his associates. Their last report [2] showed that in 33 of 35 cases selected at random there were

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From the Department of Bacteriology, the College of Medicine, the University of Cincinnati, and the Cincinnati General Hospital.

1. Blackford, S. D.: (*a*) Tularemia in Differential Diagnosis: A Review of Thirteen Cases, Virginia M. Monthly **58**:10 (April) 1931; (*b*) Pulmonary Lesions in Human Tularemia, Ann. Int. Med. **5**:1421 (May) 1932; (*c*) Pulmonary Manifestations in Human Tularemia, J. A. M. A. **104**:891 (March 16) 1935.

2. Archer, V. W.; Blackford, S. D., and Wissler, J. E.: Pulmonary Manifestations in Human Tularemia, J. A. M. A. **104**:895 (March 16) 1935.

abnormal bronchopulmonary findings. In 7 of the cases there was frank, clinically recognizable pneumonia, giving an incidence of pneumonia of 20 per cent. It is apparent that the great majority of intrathoracic tularemic lesions did not develop into gross pneumonic consolidations. Kavanaugh [3] recorded the occurrence of pneumonia in 16 of 123 cases, an incidence of 12.7 per cent.

In the first 400 cases of tularemia for which I have precise data from the date of exposure to infection to the date of complete convalescence, there were 73 cases of clinically recognizable pneumonia, an incidence of 18.2 per cent. A summation of these three series shows 96 cases of frank pneumonia in 588 cases, an incidence of 17.2 per cent. Pneumonia of moderate degree is occasionally not detectable by physical signs alone. Also, it has been my experience and that of others to find that a number of cases of "pneumonia" or of "lobar pneumonia" were actually cases of tularemic pneumonia. In some cases cocci, especially pneumococci, were notably and repeatedly absent from specimens of sputum. Most of these cases occurred in the typhoid type of the disease which had been unrecognized. This type is more frequently associated with pneumonic lesions than are the other clinical types. Hence the true incidence of tularemic pneumonia is probably a little larger than the figures indicate. At present I think a fair estimate of the incidence of pneumonia would be not less than 18 per cent.

There is, then, a fatality rate of about 6 per cent and an incidence of pneumonia of about 18 per cent. Obviously the majority of cases of pneumonia are not represented by fatalities. Even if it could be assumed that every tularemic fatality was associated with pneumonia, it is apparent that in two thirds of the cases pneumonia could not possibly have terminated fatally. Furthermore, the assumption that fatalities are always associated with pneumonic lesions is not supported by clinical and postmortem experience. As will be shown later, a large proportion of tularemic deaths occur without any clinical or necropsy evidence of such lesions. Thus the morbidity and mortality data will not support the belief that pneumonic lesions are the chief cause of tularemic deaths. These data suggest that some other lethal factor is responsible for the majority of deaths and that this other factor operates independently of the presence or absence of pneumonia.

EVIDENCE FROM A STUDY OF EIGHTY-FIVE FATALITIES

The left half of table 1 shows the distribution of my 400 cases according to the four clinical types defined by Francis.[4] It shows also

3. Kavanaugh, C. N.: Tularemia: A Consideration of One Hundred and Twenty-Three Cases with Observations at Autopsy in One, Arch. Int. Med. **55**: 61 (Jan.) 1935.

4. Francis, E.: Tularemia, Atlantic M. J. **30**:337 (March) 1927.

the frequency of pneumonia in each type and the incidence per hundred cases. It will be noted that the ulceroglandular type, the most frequent clinical form, accounts for most of the cases of pneumonia, although the incidence of pneumonia is only 15.4 per cent. It is notable that the incidence of pneumonia is significantly higher in the typhoid type. Although in only 8 per cent of cases was this clinical form presented, in 53 per cent there was pneumonia, and the type accounted for almost one fourth (23.3 per cent) of the total number of cases of pneumonia.

The right half of table 1 shows the corresponding distributions and rates in 85 fatal cases of tularemia. Data for these fatal cases were compiled from published reports, from my own cases and cases studied in consultation and from records supplied by physicians who had observed hitherto unreported deaths. A summary of these data is given

TABLE 1.—*The Incidence of the Four Clinical Types of Acute Tularemia and the Frequency of Pneumonia in Four Hundred Unselected Cases and in Eighty-Five Fatal Cases*

	400 Unselected Acute Cases				85 Fatal Cases			
Type of Tularemia	No. of Cases	Percentage	No. of Cases of Pneumonia	Pneumonia, Percentage	No. of Cases	Percentage	No. of Cases of Pneumonia	Pneumonia, Percentage
Ulceroglandular	351	87.8	54	15.4	50	58.8	25	50.0
Glandular	10	2.5	1	10.0	1	1.2	0	0.0
Oculoglandular	7	1.8	1	14.3	5	5.9	2	40.0
Typhoidal	32	8.0	17	53.1	29	34.1	21	72.4
Totals	400		73	18.2	85		48	56.5

in tables 2 and 3. Necropsies were performed in 43 cases, and pneumonia was present in 28 cases and absent in 15. In the 42 cases in which pneumonia was diagnosed by physical signs alone, it was present in 19 and absent in 18. No certain information is available in 5 cases. Here it is probable that the lack of specific record means that no pneumonia was discovered on gross examination. However, excluding these doubtful cases, it may be noted that the failure to find pneumonia by physical signs alone (in 43 per cent) is in good agreement with the failure to find it in the series in which necropsy was performed (35 per cent).

Table 1 shows that the greatest number of deaths occurred from the ulceroglandular type of tularemia, the type with the highest incidence, but that only half the total number of deaths were associated with pneumonia. Indeed, with a total incidence of pneumonia of 56.5 per cent, it is apparent that only slightly more than half of all the fatalities were associated with pneumonic lesions. Pneumonia appeared three times as frequently in the fatality as in the general series. The typhoid type

of disease appeared more than four times as frequently in the fatal cases than it did in the general group. One third of all deaths were caused by the typhoid type, and 72 per cent of deaths from this type were associated with pneumonia.

On the basis of these data it is clear that pneumonia appeared in only 56 of 85 unselected fatal cases, that pneumonia appeared in approximately the same ratio in cases in which necropsy was performed as in an equal number of cases in which it was not performed, that pneumonia appeared much more frequently in the typhoid type than in the three other clinical types, that the mortality rate of the typhoid type is significantly higher than the rates of the other types, but that this increased mortality cannot be entirely ascribed to the presence of pneumonic lesions, since in almost one third of the fatal cases of this type (29 per cent) pneumonia was not noted.

Patients with the ulceroglandular, glandular and oculoglandular types show involvement of the dermal, subdermal and regional lymphatic channels and nodes. Although Francis [4] has demonstrated that transient bacteremia occurs in the early phases of infection, the fixed lymphatic tissues seem to bear the brunt of the initial invasion in these three types. The typhoid type differs notably in this respect. There is either minor cutaneous or regional lymphatic involvement or, most commonly, none at all. In this type the infection is generalized from the onset, and multiple focal lesions are prone to develop in deep organs and tissues, especially in the lungs, with earlier impairment of important structures. The reasons for this difference are obscure, but the differential mortality rates suggest that the lack of involvement of superficial tissue in the typhoidal type might be an immunologic handicap. It may be that extensive dermal and subdermal invasion is actually of benefit to the patient and that these superficial localizations result in a stimulation of immune responses which rapidly raise the general level of tissue and humoral defenses.

Man is highly susceptible to tularemic infection, but once the disease has been acquired the great majority of patients exhibit a marked degree of natural resistance. This is borne out by the low mortality, by the histologic evidence of subacuteness and chronicity of the cellular reactions and by the infrequent establishment of chronic progressive infection. The initial bacteremia, apparently analogous to the early transient bacteremia that occurs in typhoid fever, seldom persists as septicemia, although it almost certainly is the source of a moderate number of scattered solitary foci of necrosis in various organs which, if death should supervene, are recognizable as isolated large foci, 0.5 to 1.5 cm. in diameter, most frequently in the liver, spleen and lungs.

TABLE 2.—*Synopsis of the Clinical and Postmortem Data in Forty-Three Cases*

Number of Case	Patient	Age	Sex	Type	Day of Disease at Death	Clinical Data: Pneumonia	Clinical Data: Involvement of Central Nervous System	Clinical Data: Enlargement of Liver and Spleen; Sepsis	Clinical Data: Involvement of Gastro-Intestinal Tract	Necropsy Data: Pneumonia	Necropsy Data: Involvement of Central Nervous System	Necropsy Data: Nodular Pulmonary Foci	Necropsy Data: Miliary Sepsis	Complications	Authors
1	"Jones"	62	M	U	18	0	..	+	..	0	..	+	+	.....	Hartman, Beaver and Green [17]
2	Mrs. C. S.	67	F	U	18	0	0	+	0	0	..	+	+	.....	Verbrycke [6]
3	Mrs. M. C.	35	F	G	5th mo.	+	+	0	0	0	..	+	+	Bacterial endocarditis	Francis and Callender [9]
9	?	40	M	U	18	+	0	0	0	+	..	0	+	.....	Massee [15]
14	T. M. P.	45	M	U	18	0	+	0	0	0a	+	0	+	.....	Haizlip and O'Neil [28]
15	A. R. C.	32	F	U	8	0	+	0	+	0b	..	0	+	.....	Palmer and Hansmann [13]
16	Bl. S.	37	F	U	22	+	+	+	+	+	..	+	+	.....	Foulger, Glazer and Foshay [19]
17	T. P.	32	M	T	30	+	+	..	+	+	..	+	+c	.....	Gudger [20]
20	F. W.	25	M	U	5	0	+	0	+	0	..	+	+	.....	Simpson [12]
23	V. B.	53	M	U	15	+	+	0	0	+	..	+	+	.....	Bardon and Berdez [10]
25	J. G. F.	65	M	U	14	+	+	0	0	+	..	+	+	.....	Bunker and Smith [14]
26	A. T. R.	29	M	U	14	0	..	..	..	0	..	0	+	.....	Goodpasture and House [11]
27	J. C. P.	43	M	T	16	0	+	+	+	0	..	..	+	.....	Asbury, W. D.: J. Indiana M. A. **19**: 404, 1926
30	R. S.	52	M	U	26	+	0	0?	0	Partial	..	..	+	.....	Francis, E.: Harvey Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1929
32	L. K.	24	M	U	29	0	0	+	+	0	..	0	+	.....	
38	W. S.	48	M	U	16	0	+	+	0	+	+	+	+	.....	Bryant and Hirsch [26]
39	?	50	M	U	36	0	+	0	0	0	+	+	+	.....	Hartman [27]

40	?	36	M	T	17	0c	+	0	0	+	..	+	+	.....	Permar and Maclachlan [10]
42	C. L.	57	M	U	18	+	0	+	0	+	..	+	+	.....	Lewy, R. B.†
44	M. T.	9	M	U	10	0	..	0	0	0	..	+	+	.....	Blackford [2]
45	?	45	M	T	10	+	0	+	+	+	..	+	+	.....	Simpson, W. M.†
49	T. W.	61	M	T	12	0	+	+	+	0	..	0	+	.....	Beck and Merkel [24]
50	Bl. (5)	38	M	T	41	+	0	0	0	+	..	+	+d	Pulmonary abscess	Blackford [1b]
51	Bl. (26)	23	M	T	15	+	0	0	0	+e	..	+	+	.....	
53	S. W.	53	M	U	17	+	+	..	..	+	..	+	+	.....	Gundry and Warner [23]
55	T. Th.	43	M	T	31	+	0	+	0	+	..	+	+	.....	Blackford, S. D.†
56	R.	36	M	U	26	0	0	0	0	0	..	0	0	Coronary occlusion	Kitzmiller, K. V.†
58	Z. M.	40	M	O	12	+	0	0	0	+	..	+	+	.....	Kavanaugh [3]
64	A. K.	61	F	U	16	+	0	0	0	+	..	+f	0	Aneurysm; coronary disease	Ganim, J. N.†
65	M. E. G.	53	F	T	24	+	0	0	0	+	..	+	+	.....	Bernstein [21]
66	F. P.	55	M	U	20	+	0	0	0	+	0	+	+	.....	
67	T. B. F.	52	M	U	19	+	0	0	0	+	0	+	+	.....	
69	J. S.	55	F	T	64	+	0	+	+	+	..	+	+	.....	Pessin [25]
71	A. McD.	65	M	U	90	0	+	+	0	0	..	+	+	.....	Nickerson, N. H.†
72	W. McQ.	49	M	T	15	+	+	+	0	+	..	+	+	.....	Bundeson, H.†
73	C. McC.	63	M	T	22	+	+	+	0	+	..	+	+	.....	Hull and Ikeda †
74	E. J. B.	44	M	T	13	+	?	0	0	+e	0	+	+	.....	Amoss and Sprunt [20]
76	J. H.	19	M	T	7th mo.	+	0	0	0	+	..	0	0	Miliary tuberculosis	Calder, R. M.†
77	E. C.	30	F	U	16	+	+	0	0	+	..	0	0	Bacterial endocarditis	Carroll, H. B.†
79	F. E.	56	M	T	20	+	0	0	0	+	..	+	0	Pulmonary embolism	Lewy [21]
82	W. R.	34	M	T	22	+	0	0	0	+	..	0	+g	.....	Fetterman and Lerner [30]
84	J. B.	45	M	U	10	+	0	+	0	+	0	+	+	.....	Grill †
85	J. D.	20	M	T	14	0	0	+	+	+	0	0	0?	48 hour post mortem	

* It is notable that pneumonia did not occur in the absence of signs of sepsis, except in a few cases in which death was due to some cause other than tularemia. In this table a indicates multiple infarcts; b, one small area; c, terminal; d, liver only; e, small area; f, rare, and g, spleen only.

† Unpublished data.

TABLE 3.—*Synopsis of Clinical Data in Forty-Two Fatal Cases of Tularemia in Which Necropsy Was Not Performed*

Number of Case	Patient	Age	Sex	Type	Day of Disease at Death	Pneumonia	Involvement of Central Nervous System	Enlargement of Liver and Spleen; Sepsis	Involvement of Gastro-Intestinal Tract	Complications	Authors
4	P. J. L.	37	M	O	8	0	0	0	0	.....	Freese, H. L.; Lake, G. C., and Francis, E.: Pub. Health Rep. **41**: 369, 1926
5	C. L.	7	F	O	8	0	0	0	0	.....	Freese, H. L.; Lake, G. C., and Francis, E.
6	L.	2	M	O	6	0	0	0	0	.....	Freese, H. L.; Lake, G. C., and Francis, E.
7	B. W.	37	M	U	36	0	0	+	+	Nephritis	Moloney, F. J.†
8	Fr. S.	63	M	U	47	0	0	+	+	Hypertension; nephrosclerosis	Eberly, K. C.†
10	J. W.	62	F	U	23	+	0	+	+	.....	Carothers, C. J.†
11	R. B.	36	M	T	9	+	..	+	0	.....	Foshay
12	J. T.	53	M	U	12	+	+	+	0	.....	Huether, W. W.†
13	E. B.	60	F	U	16	+	+	+	0	.....	Foshay
18	C. H.	67	M	U	17	+	+	+	+	.....	
19	S. D.	55	F	T	4th mo.	0	+	..	..	.....	Kavanaugh, C. N.: Kentucky M. J. **25**: 352, 1927
21	G. D. B.	48	M	U	9	..	..	..	..	.....	Francis, E.: De Lamar Lectures, 1926-1927, Baltimore, Williams & Wilkins Company, 1928
22	J. L.	54	M	U	12	0	?	+	+	.....	Francis, E.
24	Mrs. J. H.	58	F	U	14	0	+	?	+	.....	Rutledge, L. H.: J. A. M. A. **88**: 788, 1927
28	W. N.	58	M	U	16	..	+	..	..	.....	Francis, E.
29	J. B. S.	58	M	U	23	+	0	?	0	.....	Francis, E.
31	E. N.	40	M	U	28	0	0	0	0	Heart disease	Francis, E.
33	Fuhrer's	41	F	U	31	0	0	0	0	Heart disease	Francis, E.
34	T. J. R.	66	M	U	34	..	..	..	..	.....	Francis, E.
35	B. W. B.	31	M	U	41	+	0	?	0	.....	Francis, E.
36	C. H. W.	42	M	U	8th wk.	+	..	..	..	.....	Francis, E.
37	L. B.	32	M	U	3d mo.	0	+	?	0	Nephritis	Francis, E.
41	R. W.	..	M	U	15	?	+	?	+	.....	Pearse, R. A.: Northwest Med. **3**: 81, 1911
43	?	60	M	U	52	+	0	+?	0	.....	Boyer, S., Jr.†
46	Baby	1	F	T	4	0	+	..	+	.....	Crawford, M.: J. A. M. A. **99**: 1497, 1932
47	J.	2	M	T	6	0	+	..	+	.....	Crawford, M.
48	C.	10	M	T	28	+	0	?	+	Pulmonary abscess	Crawford, M.
52	Bl. (34)	42	F	U	16	+	?	?	?	.....	Blackford [15]
54	Ch. R.	61	M	T	15	+	0	+	+	.....	Carlson, B.†
57	L. M.	58	M	T	48	0	0	0	0	Coronary occlusion	Stout, R. B.†
59	C. C.	23	M	T	14	+	+	..	0	.....	Kavanaugh
60	W. O.	50	F	U	26	+	+	..	0	.....	Kavanaugh
61	A. G.	36	F	U	3½ mo.	+	0	..	0	Pneumothorax	Kavanaugh
62	S. D.	65	F	T	9th mo.	0	+	..	..	Nephritis	Kavanaugh
63	J. M.	34	M	T	10	+	+	?	0	.....	Foshay
68	E. H.	73	F	U	24	0	0	0	0	Coronary occlusion	Foshay
70	C. B.	23	F	U	34	+	..	..	..	.....	Cook, F. E.†
75	G. S.	31	M	T	12	+	?	0	0	.....	Amoss and Sprunt [20]
78	P. McE.	23	M	T	67	0	0	?	+	Gangrenous appendicitis	Hunt, G. O.†
80	M. R.	65	F	U	7	0	0	+?	+	.....	Huesman, A.†
81	?	28	M	U	18	0	0	+	0	.....	Preston [23]
83	G. W.	35	M	O	14	+	+	?	?	.....	Perret, J. M.†

Other common sites are lymph nodes and, possibly, bone marrow.[5] These isolated foci of necrosis may serve as points of origin of a second, later bacteremia. Also, in the lung they may initiate either florid or abortive pneumonia.

Chart 1 shows the day of disease on which death occurred in the 74 cases in which the disease terminated fatally during the first seven weeks of illness. Most deaths occurred on the sixteenth day of disease (mode, 16.4 day).

To the left of the vertical line in chart 1 are recorded a small group of deaths that occurred from the fourth to the tenth day of disease. These 14 deaths represent cases 4 to 6, 11, 15, 20, 21, 44 to 47, 63, 80 and 84 recorded in the tables. Five of these (cases 15, 20, 44, 45 and 84) came to necropsy. In only 2 (cases 45 and 84) was pneumonia present, in case 45 a single small area being noted. The pulmonary changes in case 15, described by Palmer and Hansmann as "inconsider-

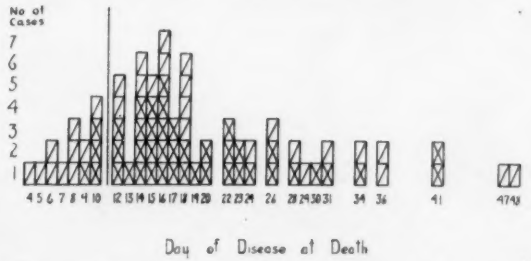

Chart 1.—Day of disease at time of death in 71 cases in which death occurred during the first seven weeks of illness. In charts 1 and 2 the crossed diagonals indicate pneumonia present at death; and the single diagonals, no pneumonia.

able," were so minor that they were regarded as insignificant as a cause of death. In the remaining 9 rapidly fatal cases, pneumonia of lobar distribution was the diagnosis in only 2 cases (cases 11 and 63). There is lack of specific record in case 21. In the other 6 cases there was no clinically recognizable pneumonia. In only 4 of the 13 cases in which there is specific record was pneumonia present. The chief necropsy observations were of myriads of submiliary to miliary focal necroses, especially prominent in the enlarged liver and spleen but also present in the lungs (in 4 cases) and to a much less extent in the serosae, kidneys, adrenal glands and other tissues. Those familiar with the postmortem appearance of small laboratory animals will agree that this brief description applies satisfactorily to the gross anatomic changes of

5. Francis, E.: Bone Marrow in Tularemia, Pub. Health Rep. **48**:1127 (Sept. 15) 1933. Yamaguchi, M.: Experimentelle Studien über die Hasenkrankheit (Yato-byo, Ohara), Tr. Jap. Path. Soc. **21**:499, 1931.

rodent tularemia. Most rodents have no natural resistance to tularemia, and in them the disease is almost invariably a fatal septicemia of brief duration, usually of from four to ten days. If the resistance is raised artificially before the animal is infected the survival period can be greatly prolonged, and the tissues then show subacute and chronic lesions comparable to those usually noted in man. Downs [6] found that rabbits partially protected by vaccination with formaldehyde-treated suspensions reacted to infection by the production of subacute lesions. By previous serial use of chemically modified vaccines and antitularemia serums I have seen chronic fibrous lesions develop in infected guinea-pigs from strains of high virulence. It seems obvious to me that this group of 14 patients (chart 1) had no natural resistance to tularemic infection and that they reacted to invasion just as normal rodents do. The clinical course in each instance was that of acute septicemia. Six patients had symptoms referable to the intestinal tract; 5 had prominent symptoms referable to the central nervous system. One child died in convulsions. Five cases occurred in children less than 10 years of age. The cause of death seems certainly to be the tularemic septicemia.

To the right of the vertical line in chart 1 are recorded deaths that occurred from the twelfth to the forty-eighth day of disease. In these cases there was evidence of some degree of resistance to the infection. A review of the clinical course in each case makes it seem improbable that death was due to sepsis resulting from the primary bacteremia, although in 3 cases there was possibility of extension of the primary bacteremia into the septicemia that preceded and apparently caused death. In the large majority of cases there was a period of variable length, usually a week or more, during which the fever was low to moderate and when symptoms and signs of intoxication, and of the extent of the disease, were no greater than those in the majority of cases of nonfatal infection. Nevertheless the postmortem observations when necropsy was performed and the antemortem clinical findings when necropsy was not performed indicate that death was preceded by, and probably caused by, septicemia. Examination of the condensed clinical and necropsy data in tables 2 and 3 will show that this is true for the great majority of fatalities. It will be noted that the exceptions fall chiefly into two classes: cases in which precise diagnostic information was unobtainable and cases in which the patient was already the victim of some other serious morbid state at the time tularemia was acquired. In the latter group cardiac disease is the most frequent. Nine deaths in this series were complicated by previous or coexisting cardiac disease.

6. Downs, C. M.: Immunologic Studies on Tularemia in Rabbits, J. Infect. Dis. **51**:315 (Sept.-Oct.) 1932.

Four patients had previous coronary disease, and 3 deaths were due to coronary occlusion that occurred during convalescence and after the fever had subsided. In only 1 of these 4 patients had anginal attacks occurred prior to the onset of tularemia. Two patients who died had complicating streptococcic subacute bacterial endocarditis, demonstrated at necropsy. Three other deaths were due to heart failure which occurred after the severe febrile phase of tularemia had been safely passed. In 2 cases the exact nature of the preexisting cardiac disease is not known. The third case was that of a patient who showed generalized arteriolar sclerosis with arteriolar nephrosclerosis, hypertension and cardiac hypertrophy and who died, afebrile, almost seven weeks after the onset of tularemia. These observations, together with others recorded elsewhere,[7] indicate that tularemia is especially dangerous to the life of the patient with preexisting cardiac disease and more especially with coronary disease. Records of additional cases of survival, with continuing attacks of angina and electrocardiographic signs of coronary disease, all with the clinical onset subsequent to tularemic infection, further emphasize this danger.

The chief clinical signs of septicemia are rapid and progressive enlargement of the liver and spleen, sometimes with steadily increasing jaundice; a temperature curve that is either continuously at a high level or of the widely swinging, daily-remittent type with high peaks; the pulmonary and constitutional signs (hyperpnea and warm cyanosis) which are usually associated with pulmonary miliary tuberculosis; signs of meningeal or cerebral involvement; diarrhea; tympanites; multiple areas of progressing bronchopneumonic lesions, usually becoming confluent; urinary findings of acute hemorrhagic nephritis or of intense acute nephrosis, and progressive involvement of the pleurae, pericardium and peritoneum.

Review of the cases reported in which necropsy was performed shows that the most constant lesions are foci of necrosis, of miliary to submiliary size, diffusely scattered throughout the liver and spleen and to a less extent in the serosae, kidneys and adrenal glands. They often occur in the lungs, with and without concomitant pneumonia. This has also been the situation in 7 of the 9 necropsies I have attended. Complicating cardiac disease was present in each of the other 2. In the cases reported by Verbrycke,[8] Francis and Callender,[9] Bardon and

7. Foshay, L., and Mayer, O. B.: Viability of Bacterium Tularense in Human Tissues, J. A. M. A. **106**:2141 (June 20) 1936.

8. Verbrycke, J. R.: Tularemia, with Report of a Fatal Case Simulating Cholangeitis, with Postmortem Report, J. A. M. A. **82**:1577 (May 17) 1924.

9. Francis, E., and Callender, G. R.: Tularemia: Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927.

Berdez,[10] Goodpasture and House,[11] Simpson,[12] Palmer and Hansmann,[13] Bunker and Smith,[14] Massee,[15] Permar and Maclachlan,[16] Hartman, Beaver and Green,[17] Kavanaugh,[3] Blackford,[18] Foulger, Glazer and Foshay,[19] Amoss and Sprunt,[20] Bernstein,[21] Preston,[22] Gundry and Warner,[23] Beck and Merkel [24] and Pessin,[25] there was ample evidence to show that septicemia preceded death. In addition, in the cases of Bryant and Hirsch [26] and Hartman [27] necrotic foci showed in the meninges and cerebral substance, respectively, and in the case of Haizlip

10. Bardon, R., and Berdez, G.: Tularemia: Report of Fatal Case with Postmortem Observations, J. A. M. A. **90**:1369 (April 28) 1928.

11. Goodpasture, E. W., and House, S. J.: Pathologic Anatomy of Tularemia in Man, Am. J. Path. **4**:213 (May) 1928.

12. Simpson, W. M.: Tularemia: Study of a Rapidly Fatal Case, Arch. Path. **6**:553 (Oct.) 1928.

13. Palmer, H. D., and Hansmann, G. H.: Tularemia: Report of Fulminating Case with Necropsy, J. A. M. A. **91**:236 (July 28) 1928.

14. Bunker, C. W. O., and Smith, E. E.: Tularemia: Report of Four Cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901 (Oct.) 1928.

15. Massee, J. C.: Tularemia in Georgia: Report of a Fatal Case, J. M. A. Georgia **20**:66 (Feb.) 1931.

16. Permar, H. H., and Maclachlan, W. W. G.: Tularemic Pneumonia, Ann. Int. Med. **5**:687 (Dec.) 1931.

17. Hartman, H. R.; Beaver, D. C., and Green, R. G.: The Occurrence of Tularemia in Minnesota in 1921: Report of Two Cases, One Fatal, with Necropsy Report, Minnesota Med. **16**:559 (Sept.) 1933.

18. Blackford.[1b] Archer, Blackford and Wissler.[2]

19. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia: Report of Case with Postmortem Observations and Note on Staining of Bacterium Tularense in Tissue Sections, J. A. M. A. **98**:951 (March 19) 1932.

20. Amoss, H. L., and Sprunt, D. H.: Tularemia: Review of Literature of Cases Contracted by Ingestion of Rabbit and the Report of Additional Cases with a Necropsy, J. A. M. A. **106**:1078 (March 28) 1936.

21. Bernstein, A.: Tularemia: Report of Three Fatal Cases with Autopsies, Arch. Int. Med. **56**:1117 (Dec.) 1935.

22. Preston, B. S.: Tularemia: Report of Fatal Case, West Virginia M. J. **27**:28 (Jan.) 1931.

23. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of a Fatal Case, Ann. Int. Med. **7**:837 (Jan.) 1934.

24. Beck, H. G., and Merkel, W. C.: Tularemia: Fatal Case of the Typhoid Form Caused by Ingestion of Rabbit; Autopsy Report, South. M. J. **28**:422 (May) 1935.

25. Pessin, S. B.: Tularemic Pneumonia, Pericarditis and Ulcerative Stomatitis, Arch. Int. Med. **57**:1125 (June) 1936.

26. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis: Report of Case, Arch. Path. **12**:917 (Dec.) 1931.

27. Hartman, F. W.: Tularemic Encephalitis: Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, Am. J. Path. **8**:57 (Jan.) 1932.

and O'Neil [25] a pure culture of Bacterium tularense was obtained from the spinal fluid by inoculation into laboratory animals. In Blackford's case 5 [1b] there was not much evidence for general septicemia, as only two microscopic foci were seen in the liver, and none were noted in the spleen. However, in addition to bronchopneumonia there were multiple foci of miliary size in the unconsolidated areas of the lungs. The appearance was similar to that of pulmonary miliary tuberculosis in which little or no bacterial dispersion occurred in the systemic circulation. In Gudger's [29] case likewise there were no foci in the liver or spleen, but there were some in the lung in addition to the pneumonia. There were clinical signs indicating involvement of the central nervous system during life, and cultures of Bact. tularense were obtained from the heart blood and from the spleen and again from the spleen by rabbit inoculation after death. This death appeared to be due to pulmonary miliary tularemic sepsis and pneumonia, with generalized terminal septicemia, in the strict sense of the term. The case of Fetterman and Lerner [30] is similar to that of Gudger, though it is not clear whether miliary foci were present in the lung in addition to the pneumonia and the large areas of caseation necrosis. Only foci of microscopic size were noted in the spleen; apparently none, in the liver. In Lewy's [31] case death occurred on the twentieth day of disease from pulmonary embolism secondary to thrombophlebitis of the inferior cava. Here also there were no signs of systemic sepsis, but miliary foci were in the lungs in addition to the pneumonia. In 13 of the 15 cases studied post mortem and reviewed by Gundry and Warner,[23] the necrotic foci were of miliary size or larger. This was also true in the necropsies attended by me. As the size of the foci is an indication of their antemortem duration, it is probable that the onset of the septicemia in these cases occurred at least four days ante mortem. In only 9 of the 15 cases was there pneumonia of sufficient extent to warrant its consideration as a cause of death. As multiple necrotic foci were observed in the liver in each case, in the spleen in every case but 1 and in the lungs in 6 cases, I believe the pathologic evidence for cause of death is much greater for death from tularemic sepsis than for death from pneumonia. The bronchopulmonary lesions are of hematogenous origin. The majority of such lesions that arise from the primary bacteremia

28. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to Bacterium Tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

29. Gudger, J. R.: Tularemic Pneumonia: Report of a Case, J. A. M. A. **101**:1148 (Oct. 7) 1933.

30. Fetterman, G. H., and Lerner, H.: Fatal Case of Tularemic Pneumonia with Associated Ileitis: Clinical and Pathologic Report, J. Lab. & Clin. Med. **21**:1157 (Aug.) 1936.

31. Lewy, R. B.: Pulmonary Tularemia, Illinois M. J. **70**:192 (Aug.) 1936.

fail to develop into pneumonic areas of any significant size. The lesser number that do become areas of frank pneumonia do not, in the absence of septicemia, become associated with fatalities but eventually are classified with the larger group (about 70 per cent) of lesions in nonfatal cases of tularemia with pneumonia. Pneumonia that arises either simultaneously with or after the onset of septicemia is certain to be recorded among fatalities. The greater frequency of pneumonia in the typhoidal type is correlated with the greater frequency of septicemia in this type. Even so, 29 per cent of deaths from this type occur from septicemia without the concomitant production of pneumonia.

In the first group of rapidly fatal cases the primary bacteremia was maintained as a septicemia which caused death. In this second group, comprising the majority of fatal cases, it is probable that the initial bacteremia did not persist, except possibly in a few cases. It is apparent then that septicemia usually arises from a second invasion of the blood stream and the origin of this second bacteremia and its causes are of great importance. Goodpasture and House [11] suggested that one mode of origin was similar to that which commonly precedes the onset of miliary tuberculosis, the erosion of a vascular wall by an encroaching necrotic focus and the discharge of its infectious contents into the circulation. Foci established by the primary bacteremia in the lungs, liver, spleen and bone marrow might well serve as points of dispersion. Also, foci established in lymph nodes by direct lymphatic extension from a primary lesion may serve similarly. Landay [32] reported a case which indicated the possibility of direct extension of bacteria through the lymphatic drainage into the venous circulation. His patient acquired a primary lesion on the right leg, just above the knee. The superficial inguinal nodes became enlarged four days later, and one progressed rapidly to suppuration and spontaneous rupture. The deep inguinal nodes also became enlarged, and soon thereafter a mass the size of a large orange appeared rising out of the right iliac fossa. This indicated rapid bacterial penetration through the superficial and deep inguinal nodes into the iliac nodes. Many patients show extension of infection from the superficial nodes of the arm to the superficial and then to the deep nodes of the axilla and thence to the subclavian or infraclavicular nodes. As such extensions are not infrequent, the likelihood of further penetration to the thoracic duct or right lymphatic duct must be rather great. Direct lymphatic extension deserves consideration as a possible mode of origin of septicemia.

This study of fatal infection indicates that the duration of tularemic sepsis is usually short, seldom exceeding ten days. The average duration of life after the onset of septicemia is about a week. It is unknown whether the defense mechanism breaks down prior to the onset of sepsis

32. Landay, L. H.: Personal communication to the author.

or subsequent to it, but observations in 450 cases after specific serum therapy lead to the belief that resistance is not lost until after sepsis has occurred. In no case in which septicemia was not present at the time serum was given did it develop. The deaths that did occur in these cases were almost never due to tularemia alone. In all instances the condition was complicated by some other disease, usually coronary heart disease, and almost all of these diagnoses were verified by necropsy. Serum therapy seems definitely to prevent the occurrence of tularemic septicemia. Furthermore, 2 patients with classic signs of general sepsis, 1 with readily palpable liver and spleen and steadily increasing icterus and the other with additional frank signs of focal cerebral lesions, have made permanent recoveries as a result of serum therapy. It is probable that the resistance of tularemic patients at this phase is similar to that of tuberculous patients just prior to the onset of miliary tuberculosis.

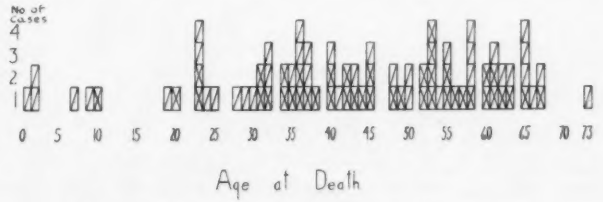

Chart 2.—Ages at death according to single years.

An important therapeutic inference arises from these studies. Most of the deaths recorded to the right of the vertical line in chart 2 were caused by tularemic sepsis occurring as a result of the second invasion of the blood stream. As the administration of antitularemia serum prevents the initiation of this septicemia, the inference is clear that had serum therapy been given early in the disease in all cases in this group, survival would have been noted in the great majority. Strong support for this reasoning is contained in records I have of cases in which treatment with serum was given on or before the twelfth day of disease. In this group were 105 cases in which no septicemia, coronary heart disease or other serious complication was noted. No deaths occurred.

A disturbing clinical feature of tularemic sepsis is that no forewarning of its occurrence is evident. It is known in general that in 1 case in every 17 sepsis is destined to develop, but at present I know of no sign or symptom that foretells its onset. I am reluctant to advise early serum therapy as a routine for a disease with such a low mortality, but at present I can see no other means of preventing these deaths. One of my fatal cases is noteworthy, as it illustrates the most treacher-

ous potentiality of tularemia, the abrupt and unpredictable onset of fatal septicemia in a patient whose symptoms up to that moment had been unusually mild.

C. H., aged 67, and his daughter-in-law, E. H., aged 32, were infected simultaneously with tularemia when cleaning wild rabbits. Each had an incubation period of three days, followed by the typical onset and course of the ulceroglandular type of tularemia, with positive agglutinin titers of 1:160 and 1:80, respectively, on the tenth day of disease. Antitularemia serum, then in its first year of clinical trial, was offered to the attending physician on the eighth and tenth days of disease but was declined on the apparently reasonable grounds that in both cases the involvement was of mild severity and the patient was doing well. On the eleventh day of disease the man's temperature rose suddenly to 104 F., after a severe chill, and his condition rapidly changed to one of the utmost gravity. About forty hours later he was admitted to the hospital. The following record was made: "The patient was semicomatose, irrational and incontinent, with continual hiccough. The temperature was 103.4 F. He could be aroused to answer questions, but he promptly lapsed into toxic delirium. There was an ulcer on the tip of the left thumb, and the nodes in the left axilla were about 4 cm. in diameter. There was no exanthem. Extreme miosis was noted. The patient was drowsy, his face was flushed and there was warm cyanosis. The liver and spleen were readily felt 3 fingerbreadths below the costal margin. Numerous râles were heard over the entire thorax, front and back. Pneumonic consolidations were noted at the base of both lungs." Sixty-six cubic centimeters of antitularemia serum had no effect on the rapidly downward course, and death occurred on the seventeenth day of disease, six and one-half days after the onset of septicemia. The physical signs of pulmonary miliary tuberculosis were interpreted as miliary tularemic focal necroses. Necropsy was not permitted, but on clinical grounds death was clearly due to tularemic sepsis. The young woman, who was admitted to the hospital on the same day as her father-in-law, never became seriously ill. She received small doses of goat antiserum and made a prompt recovery.

There is a small final group of fatal cases not hitherto mentioned. Cases 19, 37, 61, 62 and 76 are illustrative. So far as is known all the patients were healthy prior to tularemic infection, and, with the exception of one patient (case 76), all apparently died of tularemia. Deaths occurred from the third to the ninth month of disease. Progressive extension of the tularemic process to the pleurae, pericardium, peritoneum, lungs and kidneys and their sequelae, empyema, pneumothorax, peritonitis, pulmonary abscess and nephritis, appeared to account for the deaths. It is remarkable how long active, progressive lesions can persist in a few instances. These are doubtless correctly correlated with the repeated relapses, febrile and symptomatic, and often with frank recrudescences of focal lesions, that recur persistently in a few instances; in some for as long as from five to nine years after the onset. In case 76 death was due to pulmonary miliary tuberculosis. It is possible that a tularemic lesion liquefied a quiescent tubercle and ushered its contents into the circulation. Necropsy was performed, and Dr. Calder kindly sent me sections of the lungs. Every miliary and submiliary tubercle

in the section stained with carbolfuchsin showed numerous typical tubercle bacilli. No other bacteria were seen. No lesions in the sections examined could be referred to tularemia.

A study of ages at death has not yielded any new information. The frequency distribution for single years is shown in chart 2. The same data, grouped according to decades, are shown in table 4. This tends to support a growing clinical prejudice that the infection is more serious after the fiftieth year, but the series is too small to be significant. There is no marked differential mortality between the sexes.

TABLE 4.—*Frequency Distribution of Ages at Death, Grouped According to Decades*

Age, Years	Number of Deaths	Age, Years	Number of Deaths
0- 9.9	5	40-49.9	15
10-19.9	2	50-59.9	18
20-29.9	9	60-69.9	16
30-39.9	18	70-79.9	1

SUMMARY

The chief cause of death attributable to tularemia alone is septicemia due to Bact. tularense. Pneumonic lesions are present in about half the fatal cases of tularemia. Most cases of pneumonia that are associated with fatalities derive from the septicemia. Pneumonia that originates from the primary bacteremia does not become associated with fatalities unless septicemia supervenes. At least 70 per cent of the cases of tularemic pneumonia do not result in death. In a small number of patients, probably much smaller than the proportion in this series indicates, the primary bacteremia is septicemia from the onset and causes a rapidly fatal termination in from four to ten days. These unfortunate persons have apparently no natural resistance to the infection. The septicemia which causes most fatalities originates from a second invasion of the blood stream. Tularemic sepsis, with its consequent miliary focal necroses, may be generalized or may be limited to either the systemic or the pulmonary circulation. In this respect it is analogous to miliary tuberculosis. This analogy may be extended to the modes of origin of septicemia.

The mortality rate of the typhoid type of tularemia is four times that of the other clinical types. The incidence of pneumonia for this type is four times the average incidences in the three other types and is three times larger than the incidence of pneumonia in tularemia in general.

Tularemia is especially dangerous to persons with preexisting coronary heart disease. Death may occur in such cases from coronary occlu-

sion or acute myocardial failure during the initial acute phase or during early or late convalescence. The surviving patient may suffer attacks of angina pectoris, coronary occlusion and heart block for months or years after recovery from tularemia.

Persisting, progressive tularemic lesions which ultimately involve important structures are infrequent causes of death late in the course of the disease.

The third week of infection is the most dangerous period, and most deaths occur on the sixteenth day of illness. The disease is characterized by severe toxemia, which appears, of itself, seldom or never to cause death among patients who were healthy at the time tularemia was contracted. Persons over 50 years of age tolerate the infection less well than younger persons.

It is estimated that 4 of every 5 deaths from tularemia could have been prevented by the early administration of serum therapy.

PULMONARY INFARCTION COMPLICATING SEVERE DISEASE OF THE MITRAL VALVE

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An important and frequently fatal complication of severe mitral stenosis is pulmonary infarction, a complication at times difficult to diagnose and to a considerable degree neglected in medical writing. Though recognized for many years, the influence of this complication on the course of disease of the mitral valve, especially in the presence of marked congestive failure, is but little discussed in medical literature. Our attention has been recently attracted to its importance by 5 cases, 4 of the patients having been seen in the past year.

In our patients congestive heart failure, though mild at the onset, became progressively worse, and despite the therapeutic measures that were employed all 5 died within a comparatively short time. We do not think that this condition is rare, for 4 of our 5 patients were seen within a period of one year in one hospital, and we have recently encountered clinically several other patients for whom we believe the same diagnosis should have been made. One of the latter patients had marked jaundice, and although the presence of jaundice usually makes the outlook grave, this patient left the hospital in good condition.

The diagnosis of pulmonary infarction during life is not always easy, especially if there are symptoms and signs suggesting pulmonary consolidation of active rheumatic origin. The presence of pulmonary infarction should always be suspected if there is blood-streaked sputum. Also one may suspect infarction of the lungs, if congestive failure does not respond to general routine treatment, provided there are no other complications, such as masked hyperthyroidism, that may retard the effect of treatment. The presence of pulmonary infarction in severe disease of the mitral valve with congestive failure should be borne in mind as a possible contraindication for total thyroidectomy, for in these cases this radical procedure would be of no avail.

SURVEY OF THE LITERATURE

Most reports in the literature dealing with pulmonary embolism and infarction are those concerned with cases in which the condition followed a surgical procedure. Some of the reports deal with statistics

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of the presence of pulmonary infarction in medical cases. There are also a few cases of pulmonary infarction in severe disease of the mitral valve.

Muller [1] has reported the interesting case of a woman aged 40 who died of pulmonary infarction after gangrene of the left leg due to peripheral embolism; at autopsy there was noted unsuspected mitral stenosis.

Schramm [2] reported the case of a woman aged 44 with massive thrombosis of the pulmonary artery in the presence of a very large heart with mitral stenosis. In his paper he summarized the data in 3 other cases reported in the literature in which there was mitral stenosis and 5 in which there was no mitral stenosis. He said he was of the opinion that in most of these cases the pulmonary infarction was of embolic origin.

Lutembacher [3] reported 2 cases—that of a woman of 32 and that of a man of 36; in both of these cases there was "pure" mitral stenosis.

Fowler [4] reported the case of a man of 52 with mitral stenosis and pulmonary infarction. It is interesting to note that in this case the diagnosis was masked by the symptoms of the primary disease. This feature was observed in 3 of our cases.

Billings,[5] on the other hand, found reports of 16 cases of "primary" thrombosis of the pulmonary artery without mitral stenosis among the reports of 6,200 autopsies.

Boswell and Palmer [6] reported a case of pulmonary infarction without any cardiac lesion as a result of primary thrombo-arteritis of the pulmonary artery. Interestingly enough, this patient had no episodes of sudden pain.

Frothingham [7] reported a case of extensive bilateral progressive thrombosis of the smaller branches of the pulmonary artery.

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1. Muller: Gangrène du membre inferieur gauche par embolie au cours d'un rétrécissement mitral latent; amputation précoce; mort par infarctus pulmonaire, constations anatomo-pathologiques, Loire méd. **31**:321, 1912.

2. Schramm, H. G.: Beitrag zur Aetiologie der Thrombose der Arteria pulmonalis, Ztschr. f. Kreislaufforsch. **19**:713, 1927.

3. Lutembacher, R.: Thrombose de la branche droite de l'artère pulmonaire, Arch. d. mal. du cœur **26**:601, 1933.

4. Fowler, W. M.: Obliterating Thrombosis of the Pulmonary Arteries, Ann. Int. Med. **7**:1101, 1934.

5. Billings, F. T.: Primary Thrombosis of Pulmonary Artery, Pennsylvania M. J. **25**:152, 1921.

6. Boswell, C. H., and Palmer, H. D.: Progressive Thrombosis of the Pulmonary Artery, Arch. Int. Med. **47**:799 (May) 1931.

7. Frothingham, C.: Case of Extensive Bilateral Progressive Thrombosis of Smaller Branches of Pulmonary Arteries, Am. J. Path. **5**:11, 1929.

Weiss and Davis [8] found that in 9 of their 26 cases of fatal embolism in rheumatic heart disease there was marked congestive failure and in 17 there was slight or no congestive failure. They noted also in a series of 164 cases of rheumatic heart disease that the circulatory impairment often became intensified after embolism, while in some cases congestive failure developed after the accident of embolism. Pulmonary embolism and systemic embolism were not, however, differentiated.

Oberndorfer,[9] in his report from a German clinic, showed that from 1912 to 1927 there had been a decided increase in the number of cases of pulmonary embolism and thrombosis. While in 1912 there were 30 per cent among the cases in which autopsy was performed as a routine, in 1927 there were 56 (44 per cent) among 128 medical cases in which autopsy was done. He discussed four possible reasons for such an increase, namely:

1. Intravenous therapy (this etiologic factor is emphasized also by Rosenthal [10]). Oberndorfer said he thought this procedure, whatever influence it has on the course of the disease, serves as a possible factor in producing local changes either in the vessels of the arm or in the pulmonary circulation. There is little or no evidence, however, that phlebitis and venous thrombosis in the arms result in pulmonary embolism.

2. A late effect of the influenza epidemic of 1918.

3. A late effect of malnutrition as a result of the World War.

4. The greater longevity of persons with cardiac disease, due to improved therapeutic measures.

The second and third reasons are remote and unlikely. A much more plausible theory is the fourth, namely, that of longevity of persons with cardiac disease, so far as they live longer because of improved therapeutic measures. These patients go in and out of congestive failure so often that peripheral and pulmonary thromboses are not infrequent sequelae.

Zink,[11] in his analysis of the reports of autopsies at the Freiburg Pathologic Institute from January 1926 to July 1930, has shown that among 54 cases of fatal pulmonary embolism there were 38 cases in which previous hemorrhagic infarction was noted and 45 cases of pul-

8. Weiss, S., and Davis, D.: Rheumatic Heart Disease: III. Embolic Manifestations, Am. Heart J. **9**:45, 1933.

9. Oberndorfer, S.: Die Zunahme der Lungenembolien, München. med. Wchnschr. **75**:683, 1928.

10. Rosenthal, S. R.: Thrombosis and Fatal Pulmonary Embolism: Comparison of Their Frequency in the Clinics in Central Europe and North America, with Special Reference to Increase, Arch. Path. **14**:215 (Aug.) 1932.

11. Zink, K.: Der hämorrhagische Lungeninfarkt als Vorbote der tödlichen Lungenembolie, Med. Klin. **27**:1247, 1931.

monary stasis; in 9 cases there was no stasis of the pulmonary circulation. In this group of 9 cases no preceding infarction was observed. In his series, however, there were only 3 cases of mitral stenosis, and there were no comparative figures as to the frequency of pulmonary infarction in cases of hypertension.

Cabot,[12] in his observations in 200 cases of mitral stenosis, found 14 instances of embolism to various parts of the body, but he reported no cases of pulmonary infarction.

Belt,[13] in his analysis of 567 autopsy reports, found 56 cases of pulmonary embolism, 40 of which were nonsurgical. In the latter group there were 12 cases of coronary disease, 9 cases of rheumatic heart disease, 2 cases of hypertensive heart disease, 1 case of syphilitic aortitis and 1 case of pericarditis. In all cases congestive failure was present. As to the possible etiology of thrombosis, his work indicated that infection played no part, but he stated as his conclusion that slowing of the blood stream, as reported by Blumgart and Weiss, was an important factor in favoring thrombosis. He also stated the opinion that pulmonary emboli are much more common than they are generally thought to be, especially small emboli that do not cause sudden death but that may be a seat for thrombosis. These may come from the deep veins of the leg and go unrecognized. Unless careful search is made, these small emboli and infarcts will not be found.

Sheppard[14] cited Rupp, who in a statistical review of reports of 13,000 autopsies found 657 cases of pulmonary embolism and infarction of all forms and sources. In 248 of these 657 cases some kind of cardiac disease was present, but no special form was described.

Steuer,[15] in his report of 25 cases of obstruction of the pulmonary artery, listed 19 cases of thrombosis and 6 cases of embolism. In the former group there were 16 cases of congestive failure. In 5 of the 19 cases of pulmonary thrombosis there was auricular fibrillation; there were 13 cases of hypertension, 1 case of rheumatic heart disease, 3 cases of cardiovascular syphilis and 2 of disease of the coronary arteries. Among the 19 cases of thrombosis there were 13 cases (68 per cent) of pulmonary infarct. Among the 6 cases of embolism, there were 3 cases of disease of the mitral valve, 1 case of hypertension, 1 of

12. Cabot, R. C.: Mitral Stenosis: Observations on Two Hundred Cases Before and After Death, Also on One Hundred and Sixteen Not Autopsied, Tr. A. Am. Physicians **29**:22, 1914.

13. Belt, T. H.: Thrombosis and Pulmonary Embolism, Am. J. Path. **10**: 129, 1934.

14. Sheppard, T. T.: Pulmonary Embolism and Infarction, Atlantic M. J. **27**:588, 1923.

15. Steuer, L. G.: Embolism and Thrombosis of Large Branches of Pulmonary Artery in Heart Disease, J. Lab. & Clin. Med. **19**:265, 1933.

syphilis and 1 of disease of the coronary arteries. His conclusions were that hypertensive heart disease was most frequently associated with pulmonary thrombosis, while rheumatic heart disease was most frequently associated with pulmonary embolism. "In conclusion," he stated, "it can be said, that in a case of prolonged cardiac failure with repeated indications of pulmonary infarction, embolism or thrombosis of the pulmonary vessels may be anticipated."

Hosoi,[16] in his analysis of 810 reports of necropsies from 1921 to 1929, found 64 cases of pulmonary embolism, 36 of which were medical cases. In the latter group there were 4 cases of congestive failure.

Farr and Spiegel[17] from their study of 32 cases of pulmonary embolism with infarction between 1881 and 1927 concluded:

1. In spite of stasis, which in some cases is generalized, primary thrombosis in the peripheral veins as a source of pulmonary infarction is rare. They noted only 1 case in which the veins of the leg may have been the source.

2. Pulmonary infarction is not necessarily embolic. Passive congestion plays an important rôle.

Farr and Spiegel further stated that the pulmonary involvement plays but a minor part in the severity of the condition but is of prognostic value because it reflects the extent of the failure of the right side of the heart. In their series there were 22 cases of cardiovascular origin, but no mention was made either of congestive failure or of what valves were involved.

Two clinical pictures of pulmonary infarction have been described in the textbooks and recently emphasized by Sheppard.[14] In one there is a sudden episode of sharp pain in the chest followed by hemoptysis. This type may occur in severe disease of the mitral valve, with or without congestive failure. If congestive failure is not present, a satisfactory recovery is frequently made. Examination usually reveals evidence of consolidation, and not infrequently this is mistaken for lobar pneumonia. In a great majority of cases a pleural friction rub is heard, and this is considered by many to be a part of the pneumococcic infection. Not infrequently one may find such an episode in the presence of congestive failure. In these instances the diagnosis is not difficult.

The second type that has been described occurs in severe disease of the mitral valve with congestive failure and consists of a sudden severe attack of hemoptysis, with or without ensuing pain in the chest. Occasionally one will encounter a case in which there is severe pulmonary edema but little evidence of consolidation, as in the previous type.

16. Hosoi, K.: Pulmonary Embolism and Infarction: Analysis of Sixty-Four Verified Cases, Ann. Surg. **95**:67, 1932.

17. Farr, C. E., and Spiegel, R.: Pulmonary Infarction and Embolism, Ann. Surg. **89**:481, 1929.

Although pulmonary infarction is frequently considered to be of embolic origin, there are numerous instances in which local changes in the pulmonary arteries are the only positive findings.

REPORT OF CASES OF PULMONARY INFARCTION COMPLICATING DISEASE OF THE MITRAL VALVE WITH CONGESTIVE FAILURE

In 4 of our 5 cases there was no history of hemoptysis at any time, while in the fifth case, though there was a history of hemoptysis several years prior to the onset of the present illness, when congestive failure set in there was no evidence of hemoptysis. The main feature in all our cases was the impossibility of controlling the increasing congestive failure. The difficulty of making the diagnosis of pulmonary infarction in such cases is due to the fact that the cardiac symptoms overshadow those due to the infarction. Occasionally the pulmonary symptoms are so severe that unsuspected mitral stenosis is overlooked, as in the case reported by Muller.[1]

In 3 of our 5 cases there was a normal cardiac rhythm and in 2 auricular fibrillation; interestingly, in none of these 5 cases was there evidence of a thrombus in the heart at postmortem examination. There was suggestive evidence of active rheumatic heart disease in 2 cases, while in the other 3 there was no evidence of such activity. All 5 patients were women; their ages were 36, 41, 19, 51 and 29 years, respectively.

CASE 1.—Mrs. E. van D., aged 36 years, entered the hospital on Sept. 6, 1934, and died on October 14. The family history was unimportant. There was no history of rheumatic fever. Curettement of the uterus was performed in 1930 and in 1932. There had been increasing dyspnea since the spring of 1932 and swelling of the feet and abdomen for the past month. There had also been a dry cough for two years without hemoptysis.

On physical examination there were a low-pitched rumble throughout diastole, a sharp first sound at the apex of the heart and moderate engorgement and pulsation of the cervical veins. The cardiac rhythm was normal. There was dulness at the base of both lungs, with moist râles up to the midcapsular region. The liver was enlarged and tender. The abdomen was tender, with dulness in the iliac region. There was edema of the abdominal wall and of the sacrum.

Course.—The congestive failure gradually yielded to the effect of digitalis and diuretic drugs, and the patient was entirely free from edema when she began to suffer from gradually increasing dyspnea, with fever leading to death in a few days. Dulness and bronchial breathing were noted at the base of the right lung.

Diagnosis.—The clinical diagnosis was rheumatic heart disease, mitral stenosis and pulmonary infarction.

Postmortem Examination.—At autopsy the heart showed much enlargement of the right ventricle and left auricle, with increased thickness of the walls. The pulmonary artery was free. There was no pericarditis or acute endocarditis. No Aschoff bodies were seen. There were no thrombi in the auricles. The left lung

was normal. The right lung was infarcted, the infarct involving three quarters of the lower lobe and one third of the middle lobe. The infarct in the lower lobe extended 11 cm. upward from the diaphragmatic surface in back and 4.5 cm. upward from the diaphragmatic surface in front. The infarct in the middle lobe was in the lateral part. There was bronchopneumonia around the infarcted areas. There was an adherent thrombus in the artery to the lower lobe of the right lung, with slight change in the wall of the artery at the distal end of the thrombus and an extension of the thrombus back several centimeters to include the whole of the blood supply to the lower lobe and part of that to the middle lobe.

CASE 2.—Miss J. E. J., 41 years of age, a teacher entered the hospital on Feb. 11, 1935, and died on February 14. The family history was unimportant. The patient was first seen by one of us in 1932, and examination then showed mitral stenosis. There was slight cardiac enlargement, the presence of which was proved by roentgenograms. She was well until two weeks before entrance to the hospital, when sore throat developed with a temperature of 101 to 102 F. There was no cough or hemoptysis.

Physical examination revealed evidence of consolidation of the lower lobe of the right lung, with some congestive failure, as shown by hepatic engorgement and distention of the cervical veins. The cardiac rhythm was normal. There was marked mitral stenosis.

Course.—Three days after the patient's entrance to the hospital there were râles and bronchial breathing in the left axilla, but no friction rub. There was increasing edema before death.

Diagnosis.—The clinical diagnosis was rheumatic heart disease, mitral stenosis and (?) rheumatic pneumonia.

Postmortem Examination.—At autopsy there was slight enlargement of the heart (weight, 350 Gm.). The right ventricle was markedly hypertrophied and dilated. The mitral valve was markedly stenosed, with short chordae tendineae, and there was a question of fresh vegetations on the aortic valve. The pericardium showed several hemorrhagic spots over the anterior surface near the interventricular sulcus. There were no thrombi in the auricles. The lungs showed six or eight hemorrhagic infarcts, with thrombosis of the pulmonary vessels leading to them in at least 2 instances. Grossly the vessels were normal.

Microscopically no Aschoff bodies were seen in the myocardium, but in a section of the mitral valve at the base there was seen a collection of cells having rare vesicular nuclei, similar to plasma cells, constituting a focus which was thought to be an Aschoff body.

CASE 3.—Miss B. M., aged 19 years, entered the hospital on Dec. 6, 1934, and died on December 10. The family history was unimportant. There was no history of rheumatic fever. Tonsillectomy had been performed in 1929.

For seven years before her entrance to the hospital, during routine examinations at school, she was told she had a heart murmur. During the summer of 1934 she had an attack of coughing. In August, while swimming, she had an attack of palpitation which was apparently due to auricular fibrillation, with a heart rate of 120 to 130. The fibrillation persisted in spite of the use of digitalis, without change in the heart rate, except on one occasion, when it dropped to 80.

Physical examination on November 27 at her home showed evidence of slight arterial pulsation in the neck. The heart was markedly enlarged to the left and downward. The rhythm was irregular. There were present the murmurs of mitral

stenosis and regurgitation. The lungs were clear. Examination of the abdomen revealed that the edge of the liver was palpable 2 fingerbreadths below the costal margin. There was no dependent edema.

Course.—On December 6 the patient's condition became much worse; the heart rate rose to 140 or more and the temperature to 104 F. Gradually there was increasing congestive failure, and she died on December 10.

Postmortem Examination.—Autopsy showed enlargement of the heart due to hypertrophy and dilatation. The heart weighed 325 Gm. All the valves were normal, except the mitral valve, which was deformed but not stenosed. There were short chordae tendineae and thickening of the line of closure and at the edge of the valve. There were no antemortem intracardiac clots. There were no vegetations. Over the pericardium, pleurae and peritoneum there were several small hemorrhagic areas, and in the right lung there were several areas of hemorrhagic consolidation, resulting in a diagnosis of pulmonary infarct (?) and rheumatic pneumonia (?).

Microscopic examination showed that the vessels throughout the myocardium were markedly congested. There were a few foci where the muscle fibers were fragmented and often replaced by a homogeneous, pink-staining substance over which there were a few oval nuclei without any cell membrane. Around some of the larger vessels there was an occasional but only slightly suggestive Aschoff body.

CASE 4.—Miss M. W., aged 51 years, entered the hospital on May 2, 1934, and died on May 14.

Her complaint was of constricting pain in the upper portion of the abdomen of six years' duration and more recent orthopnea. She had had rheumatic fever every winter when between the ages of 3 and 14 years. There had been discomfort in the upper portion of the abdomen for the past six years, and there had been increasing dyspnea for two or three years. The heart beat had been irregular since 1930, at which time she was in bed for seven weeks. She had been taking digitalis since 1931. There was a slight cough, brought on by the dyspnea. In May 1931 an examination showed a blood pressure of 150 systolic and 100 diastolic, auricular fibrillation (with a ventricular rate of 80), a rumbling mid-diastolic and a late diastolic murmur at the apex and fine moist râles at the base of the right lung.

Physical examination on May 2, 1934, showed a blood pressure of 140 systolic and 90 diastolic, a heart rate at the apex of 92 and a radial pulse rate of 84. The heart was described as noted previously. Examination revealed some pleural fluid at the base of the right lung. The liver was very tender and extended 4 or 5 fingerbreadths below the costal margin. There was cyanosis of the lips, with pallor of the nails.

Course.—There were increasing edema and dyspnea, despite the use of diuretics. The patient died on May 14.

Postmortem Examination.—At autopsy the mitral valve was markedly calcified and thickened, with a fish mouth opening 2 cm. in length. There were two pulmonary infarcts. The pleural surfaces were mottled blue and gray, except for an irregular area in the lower lobe of the left lung, which was dark red, and a small rounded area in the anterior surface of the upper lobe of the right lung, which also was dark red. The lower lobe of the left lung showed a roughly cone-shaped area which was firm and reddish black, about 4 cm. in diameter at its base and 5 cm. in height. The upper lobe of the right lung showed another cone-shaped firm area, 1.5 cm. in diameter at the base and 2 cm. in height.

CASE 5.—J. R., a woman, aged 29 years, entered the hospital on Dec. 1, 1931, and died on December 4.

Her father had died of disease of the coronary arteries. Her past history was unimportant, except for "growing pains" in childhood.

For nine years prior to entrance to the hospital the patient had coughed up blood on several occasions, but at no time was there congestive failure, until six months before her admission to the hospital, when edema of the legs was first noticed. There was no hemoptysis after the onset of congestive failure. There was also a nonproductive cough.

Physical examination revealed cyanosis and orthopnea. There were mid-diastolic and presystolic murmurs at the apex of the heart. There was marked cardiac enlargement. There were impaired resonance over the base of the right lung, bronchovesicular breathing on the right in the middle of the back, distant breathing at the base of the right lung and a few râles at the base of each lung.

Course.—Digitalis and salyrgan had no effect on the increasing edema. Death occurred three days after the patient's entrance to the hospital.

Postmortem Examination.—Autopsy showed the right ventricle to be dilated. The heart weighed 500 Gm. There were no fresh vegetations on the mitral valve, but there were some on the atrial side of the tricuspid valve. No Aschoff bodies were present in the myocardium. The visceral and parietal surfaces of the pericardium showed many petechial spots. There were areas of infarction in the upper and lower lobes of the right lung, as well as a few smaller nodules in the periphery of the lower lobe of the left lung. The right pulmonary artery contained an elongated, ragged, red antemortem clot progressively filling the lumens of several of the smaller branches of the pulmonary artery. The upper three quarters of the upper lobe and the upper half of the lower lobe of the right lung, as well as two distinct small areas in the lower lobe of the left lung, were infarcted.

STATISTICAL STUDY OF THE INCIDENCE OF PULMONARY INFARCTION IN DISEASE OF THE MITRAL VALVE AT THE MASSACHUSETTS GENERAL HOSPITAL

To determine the frequency of pulmonary infarction in severe disease of the mitral valve, all the cases in which autopsy was performed at the Massachusetts General Hospital over a period of fifteen years and in which a diagnosis of mitral stenosis was made were investigated, and a comparative study was made with cases in which the diagnosis was hypertensive heart disease. The accompanying tables show how frequently mitral stenosis is complicated by pulmonary infarction. It will be noted that in 23 of the 52 cases of severe mitral stenosis there was congestive failure. In this group of 23 cases there were 14 (61 per cent) in which pulmonary infarction was a complication, while in 9 (39 per cent) there was no infarction. There were 27 cases of mitral stenosis without congestive failure and without infarction. In 2 cases there was no congestive failure with infarction. These 52 instances were found in the records of 2,500 autopsies performed between 1919 and 1934.

In the records of 1,400 autopsies performed from 1930 to 1934 there were 82 cases of hypertension. In 39 of the 82 cases there was congestive failure, in 8 cases (21 per cent) infarction being present, as compared with 61 per cent for the cases of rheumatic heart disease. Thus there were 31 cases (79 per cent) of congestive failure without infarction. In the 43 remaining cases in which congestive failure was not present, there were 5 cases of pulmonary infarction and 38 cases in which there was no infarction.

TABLE 1.—*Cases of Mitral Stenosis Among the Records of 2,500 Autopsies at the Massachusetts General Hospital, 1919 to 1934*

	No. of Cases	Percentage
Mitral stenosis and congestive failure with pulmonary infarction..	14	61
Mitral stenosis and congestive failure without pulmonary infarction	9	39
Mitral stenosis without congestive failure and with pulmonary infarction	2	7
Mitral stenosis without congestive failure and without pulmonary infarction	27	93
	52	

TABLE 2.—*Cases of Hypertension Among the Records of 1,400 Autopsies at the Massachusetts General Hospital, 1930 to 1934*

	No. of Cases	Percentage
Hypertensive heart disease and congestive failure with pulmonary infarction	8	21
Hypertensive heart disease and congestive failure without pulmonary infarction	31	79
Hypertensive heart disease without failure and with pulmonary infarction	5	12
Hypertensive heart disease without congestive failure and without pulmonary infarction	38	88
	82	

COMMENT

Pulmonary infarction as a complication of severe disease of the mitral valve, especially in the presence of congestive failure, is not infrequent, as shown by the statistics in the accompanying tables. Four of the 5 new cases reported were discovered by us in the course of one year, and doubtless in more cases this diagnosis would have been made had an autopsy been performed.

It is important to recognize this complication, not only from the standpoint of greater diagnostic accuracy but because its recognition indicates with a fair degree of certainty that the prognosis is grave.

Although in the 5 cases reported here the outcome was fatal, we have noted cases in which the patient recovered, including even a recent case

in which there was considerable jaundice, usually a grave sign. Jaundice, when it does occur in these cases, is of hemolytic nature, due to the sudden excessive burden on a congested and perhaps otherwise damaged liver of disposing of the large amount of blood pigment in the pulmonary infarct.

The presence of pulmonary infarction retards all forms of treatment for congestive heart failure.

There are four possible sources of pulmonary infarction:

1. Thrombosis in situ may be the source. This may be favored by such pulmonary arteriosclerosis as was noted by Brenner [18] in his study of the pathology of the pulmonary circulation, which is almost certainly favored by the sluggish circulation in the dilated pulmonary vascular system. With increasing congestive failure in cases of mitral stenosis, resulting in a sluggish and engorged pulmonary circulation, it is possible for a thrombus to form in the pulmonary arterial system. After this sequence, pulmonary infarction is likely to take place.

2. Embolism from concealed thrombosis in veins of the abdomen, pelvis or legs, as shown by Homans,[19] is another possible source of pulmonary embolism. The search for emboli in the veins of the legs as a possible source is a tedious process, and on this continent a thorough search is rarely made; not infrequently cases are overlooked, and the source of the pulmonary infarction is undetermined.

3. Embolism from thrombi in the chambers of the right side of the heart is prone to occur, especially in the presence of auricular fibrillation. This is particularly true when the circulation has been greatly retarded. However, in our series, although in 2 cases auricular fibrillation had been noted, none of the hearts showed any evidence of thrombi in the auricles or ventricles at autopsy.

4. Acute infection superimposed on an old rheumatic lesion may be a possible source of pulmonary infarction, especially in younger persons. In 2 of our cases there were structures suggestive of Aschoff bodies in the cardiac valves, indicating the location of the possible source. This theory was emphasized in 1858 by de Zumann, as quoted by Giroux.[20]

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18. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:211 (Aug.); 547 (Sept.); 724 (Oct.); 976 (Nov.); 1189 (Dec.) 1935.

19. Homans, J.: Thrombosis of Deep Veins of Lower Leg Causing Pulmonary Embolism, New England J. Med. **211**:993, 1934.

20. Giroux, L.: Sclérose et athérome de l'artère pulmonaire; rôle des conditions mécaniques, Thèse de Paris, no. 149, Paris, G. Steinheil, 1910.

Pulmonary infarction as a clinical picture presented in our series of 5 cases has not been well recognized as such: that is, a clinical picture of intractable pulmonary embarrassment without any sudden episode in the presence of severe disease of the mitral valve and congestive failure. This type of complication may or may not be accompanied with evidence of pleural friction. One should always bear in mind that in these cases the clinical syndrome of a sudden vascular accident is not necessary for the diagnosis of pulmonary infarction.

SUMMARY AND CONCLUSIONS

We report here 5 cases of severe disease of the mitral valve with congestive failure having as a fatal complication pulmonary infarction without any clinical syndrome of sudden vascular collapse or any similar episode. Autopsy was performed in each case.

Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis noted in 2,500 records of autopsies at the Massachusetts General Hospital showed that pulmonary infarction occurred in 61 per cent of 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension noted in the records of 1,400 autopsies at the Massachusetts General Hospital, there were 39 cases of congestive failure, in 21 per cent of which there was pulmonary infarction.

Pulmonary infarction complicating severe disease of the mitral valve with congestive failure is not uncommon. This condition is sometimes difficult to diagnose; it makes treatment of the congestion very difficult, and it renders the prognosis grave.

MONOCYTIC LEUKEMIA

CUTANEOUS MANIFESTATIONS OF THE NAEGELI AND SCHILLING TYPES; HEMOCYTOLOGIC DIFFERENTIATION

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AND
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It is important to distinguish between the so-called Naegeli type of monocytic leukemia (which many regard as a variant of myelogenous leukemia, with predominance of monocytes) and the true Schilling type (leukemic reticulo-endotheliosis), in which the cells are derived from the reticular cell. A primary autochthonous cutaneous origin for either type of monocytic leukemia may be encountered, a fact which we believe is not generally recognized by internists and pathologists or even by many dermatologists. One of us (H. M.)[1] has previously emphasized the possible autochthonous cutaneous origin of any of the lymphoblastomas, including even myelogenous leukemia.[2]

It is not pertinent in this paper to discuss the various hemocytologic views regarding the monovalent, dualistic and trivalent origin of leukocytes.[3] There is an increasing tendency in the recent literature to recognize two types of monocytic leukemia as well as the lymphatic and myelogenous types of leukemia. If one accepts the point of view that

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From the Section on Dermatology and Syphilology and the Division of Medicine, the Mayo Clinic.

1. Goeckerman, W. H., and Montgomery, Hamilton: Cutaneous Lymphoblastoma: Report of Two Unusual Cases, Arch. Dermat. & Syph. **24**:383-395 (Sept.) 1931. Montgomery, Hamilton: Exfoliative Dermatosis and Malignant Erythroderma: The Value and Limitations of Histopathologic Studies, ibid. **27**: 253-271 (Feb.) 1933; Mycosis Fungoides, Lymphoblastoma of the Skin, and Allied Conditions as General Diseases, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1936, vol. 4, pt. 1, chap. 1A, pp. 44(1)-44(19).

2. Barney, R. E.: Leukemic Myelosis Associated with Specific Nodules in the Skin: Report of a Case and Review of the Literature, Arch. Dermat. & Syph. **27**:725-738 (May) 1933.

3. Kracke, R. R., and Garver, Hortense: The Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types, J. A. M. A. **104**:697-702 (March 2) 1935. Wiseman, B. K.: The Origin of the White Blood Cells, ibid. **103**:1524-1529 (Nov. 17) 1934. Wiseman, B. K.; Doan, C. A., and Erf, L. A.: A Fundamental, Reciprocal Relationship Between Myeloid and Lymphoid Tissues: Its Recognition, Nature and Importance as Revealed by Experimental and Clinical Studies, ibid. **106**:609-614 (Feb. 22) 1936.

reticular cells (reticulo-endothelial cells) and monocytes can give rise to lymphocytes, then all the aforementioned conditions and also mycosis fungoides may be grouped under the term lymphoblastoma, with recognition of the fact that it is important to distinguish between these different types until more is known regarding their etiology.

We wish to report five cases of monocytic leukemia with cutaneous manifestations, two of the Naegeli and three of the Schilling type. Primary autochthonous cutaneous involvement occurred in one or possibly two cases of the Schilling type and in one case of the Naegeli type, as contrasted with secondary terminal cutaneous lesions in the other two cases, one of each type.

NAEGELI TYPE

CASE 1.—A man aged 45 was first seen at the clinic in 1921, because of gastric distress for thirty years. Thorough examination failed to reveal any organic cause for his complaints. He was reexamined in August 1924, at which time a diagnosis of probable duodenal ulcer was made.

When the patient was seen for a third time, in 1928, the diagnosis was chronic nervous exhaustion, constipation and functional dyspepsia. The results of laboratory examinations were all within normal limits. The patient at this time complained of eczema of six weeks' duration, which had begun on the legs and had soon become generalized. Biopsy of one of the lesions from the shoulder revealed a dense infiltrate with many reticulum cells and other features of lymphoblastoma, although the picture was not diagnostic as to type. There was nothing abnormal about the hemocytologic picture.[3] Roentgen treatment was given over the neck, mediastinum, pelvis, back and groins.

The patient returned to the clinic again in March 1929, at which time the plaques on the skin were more infiltrated and the picture was more suggestive clinically of mycosis fungoides. Another biopsy revealed a greater degree of infiltration, with multiplicity of cell types. There were also many lymphocytes and occasional monocytes and endothelial cells. There was a definite increase in reticulum (*Gitterfasern*, or lattice fibers). The histopathologic picture was not specific as to the type of lymphoblastomatous involvement. Further roentgen treatment was administered.

We saw the patient again in April 1932, when he had two plaques in the left pectoral region and one on the left forearm. Nodular infiltrations and necrotic ulcers also were present (fig. 1). Biopsy at this time revealed a more active process, with a number of mitotic figures, so that both Dr. Broders and one of us (H. M.) favored the diagnosis of mycosis fungoides bordering on lymphosarcoma. There was a definite increase in the number of monocytes and reticulum cells but no more than one would expect to see in a case of mycosis fungoides. The hemocytologic observations were again within normal limits. Additional roentgen treatment was given.

The patient returned to the clinic once more, in September 1932, at which time the condition of the skin was much improved. He had, however, lost 15 pounds (6.8 Kg.). He had had recurring attacks of conjunctivitis and painful swelling, with local heat and fever in various parts of the body. He was hoarse, and there were edema and redness of the vocal cords which epinephrine did not relieve. Roentgenograms of the thorax, stomach and skull were normal, and blood cultures

were sterile. The hemocytologic observations were as follows: marked poikilocytosis, much basophilic stippling, an occasional normoblast and definite immaturity in the myeloid line back to the myeloblast or stem cell, with predominance of differentiation along the monocytic line. It was suggested that the condition was probably monocytic leukemia.

The patient was given a blood transfusion and experienced a subsequent febrile delayed reaction. The value for serum bilirubin and tests of hepatic function were normal. Prostatitis of grade 3 was present. Studies of the blood later in September revealed severe anemia, with the number of normoblasts increased over

Fig. 1 (case 1).—Nodules and necrotic ulcers on the forearm and chest.

that of the previous smear, more immaturity and more marked predominance of monocytes, with all stages of differentiation from the myeloblast or stem cells. A diagnosis of monocytic leukemia of the Naegeli type was thus established. Further hemocytologic studies confirmed these observations. Unfortunately no specimen of skin was taken for biopsy at this time, nor were specimens from the bone marrow or the costal cartilage examined. The patient went downhill rapidly and lost weight, and there was evidence of progression of the anemia. The spleen could not be felt, and there was no enlargement of the lymph nodes. Recurring areas of inflammation were present in the extremities, conjunctiva and chest, as well as hemorrhagic lesions. Pericardial friction rub, stupor and urinary reten-

tion developed, and the patient died on October 24. Postmortem examination confirmed the diagnosis of monocytic leukemia of the Naegeli type. There were fibrinous pericarditis and terminal bronchopneumonia, but the infiltrate in the lungs was composed chiefly of monocytic cells rather than leukocytes. There was grade 4 proliferation of the mediastinal nodes, and numerous monocytes were present. The spleen showed proliferation of reticulo-endothelial cells and numerous monocytes. The mesenteric nodes revealed hyperplasia of grade 3. The bone marrow contained large numbers of mature and immature neutrophils, myelocytes, monocytes and eosinophils.

CASE 2.—A man aged 51 was examined at the clinic in September 1929, because of an enlarged lymph node in the neck, which had been present for six weeks. He had influenza in December 1928, but the gums remained sore, and pain developed in the chest and back. In March he began to become weak on exertion. Tonsillectomy was performed five weeks before his admission to the clinic, and afterward the lymph nodes became enlarged.

Examination revealed hypertrophy of the gums, mucous membranes and soft palate, the palate being swollen and edematous. All the lymph nodes in the neck were enlarged, tender, discrete and movable. The liver was palpable 4 cm. below the costal margin; the spleen, too, was palpable. There were paralysis of the left side of the face (Bell's palsy) and a fading purpuric eruption limited to the thighs and legs but no infiltration suggesting leukemids. The patient was hospitalized. The hemocytologic observations were as follows: marked poikilocytosis, with much basophilic stippling, increased regenerative activity, definite myeloid immaturity back to the stem cell and marked predominance of monocytes. This was the picture of monocytic leukemia of the Naegeli type.

A month later the patient presented small nodular lesions, subacutely inflamed, which were limited to the right thigh and both shins; these strongly suggested leukaemia cutis. Biopsy revealed a definitely lymphoblastomatous picture, there being many large immature cells and also many monocytes. There was no evidence of lymphosarcoma or Hodgkin's disease. The patient died at home, and some of the organs were sent to the clinic for examination. Pathologic examination revealed marked hyperplasia of the bone marrow, myeloblasts and monocytes predominating. Numerous mitotic figures were present, indicative of an active process. There was no increase in free reticular cells. A similar picture was seen in a clot in the portal vein, in the splenic pulp and in the sinuses of a lymph node. The lymphoid tissue was not hyperplastic.

SCHILLING TYPE

CASE 3.—A retired butcher aged 62 was first seen at the clinic on April 8, 1935, because of a cutaneous condition which had begun in March 1931 with itching on the inner aspect of the thigh and on the flexural surface of the arm. The hands had become involved in the summer of 1931 and the feet in 1932. The process extended to the flexures and volar surfaces of the forearms and the mesial aspects of the thighs. The extent and severity of the eruption had fluctuated, but the condition had never cleared up entirely.

Examination at the clinic revealed generalized thickening and lichenification of the skin and dry eczematous patches. The palms and soles showed marked hyperkeratotic scaling processes, with fissuring and heaping up under the free edge of the nails. There was definite lymphadenopathy in the groin. A diagnosis of mycosis fungoides was made, and a specimen for biopsy was taken from the plaque near the axilla. The histopathologic picture had many of the features of mycosis

fungoides (fig. 2*A*), but later review of the sections revealed that a few of the lymphocyte-like cells presented notched serration and also grooving of the nuclei. The hemocytologic picture was similar, but there was insufficient evidence to

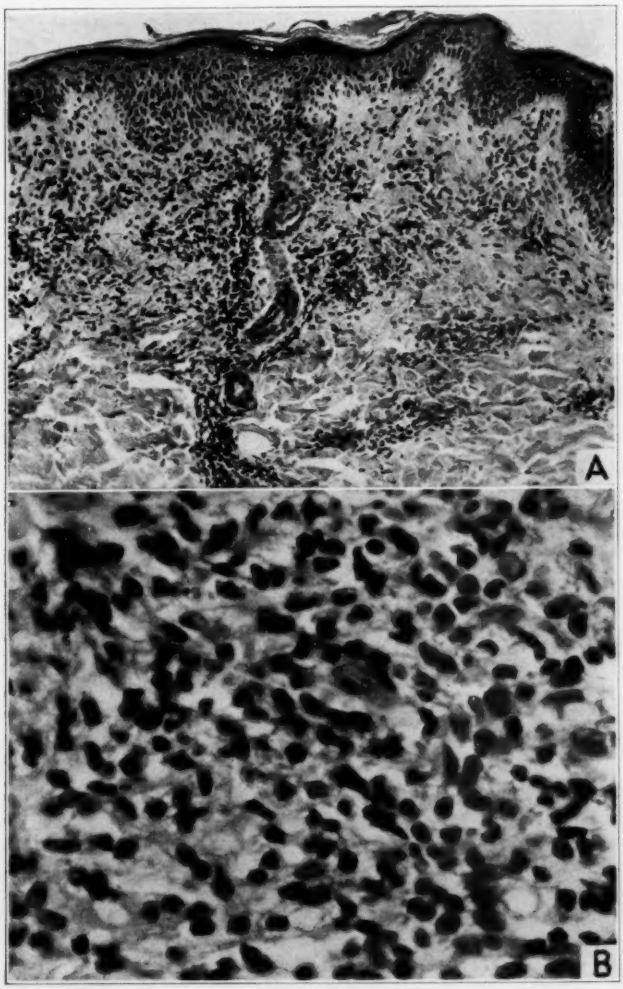

Fig. 2 (case 3).—*A*, the histologic picture suggests mycosis fungoides (April 1935). *B*, the specific infiltrate in the skin of monocytic cells, many of which show definite grooving or serrated indentation of their nuclei (June 1936).

establish a diagnosis of monocytic leukemia of the Schilling type.[2] Smears made from the specimen taken for biopsy and blood smears also revealed identical pictures. There was an increase in *Gitterfasern* in the specimen of skin. Roent-

genograms of the thorax as well as a general examination revealed no abnormality. The patient was given a course of roentgen therapy, and he obtained considerable relief from the itching.

The patient returned in June 1936, at which time he presented more the clinical picture of exfoliative dermatitis (fig. 3). He had had eight roentgen treatments at home, the last one in February. A specimen taken for biopsy revealed a some-

Fig. 3.—*A*, marked exfoliative dermatitis, later becoming erythroderma (case 3). *B*, the extent of the purpuric lesions throughout the skin of the entire body (case 5).

what denser infiltrate, with many definitely monocytic cells (of the Schilling type), both with indentations of nuclei and also with grooving through the nuclei (fig. 2*B*). No clumping of cells, pyknosis or karyorrhexis of individual cells, such as characterizes mycosis fungoides, was seen in the second specimen for biopsy. The hemocytologic observations were as follows: leukemic reticulo-endo-

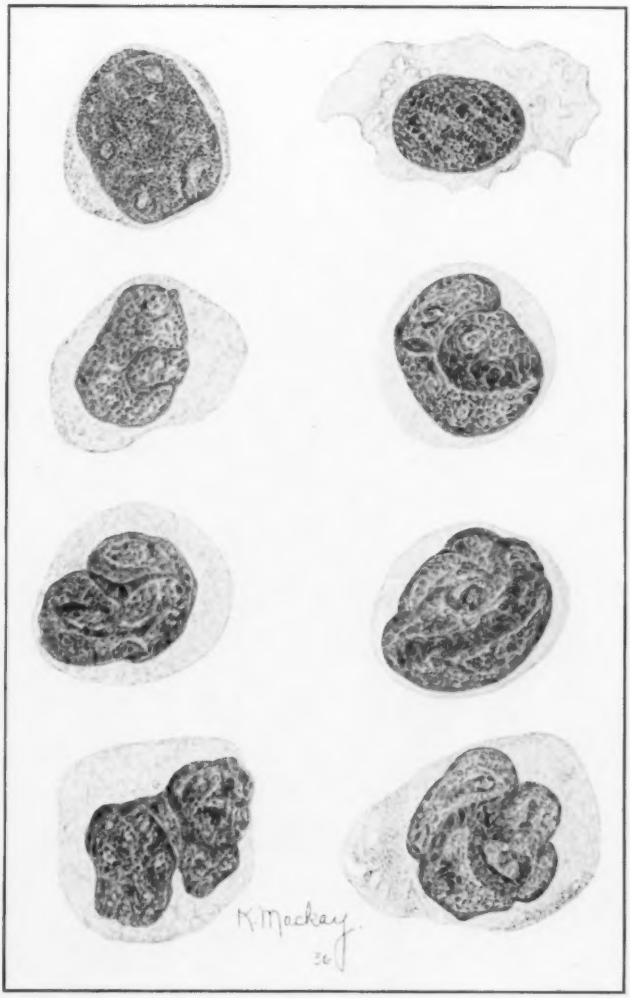

Fig. 4.—The difference between the various types of cells in monocytic leukemia: The left column, Naegeli type, from top to bottom illustrates the changes from the myeloblast to the relatively mature monocyte. The right column, Schilling type, represents stages in the development from the reticular cell to the mature monocyte.

theliosis, with monocytes showing definite grooving and intermediate stages of development back to primitive cells, with characteristics of the reticular cell. A diagnosis of monocytic leukemia of the Schilling type was made. On September 13 the patient was presented before the Mississippi Valley Dermatological Society. He then had mild, generalized residual erythroderma. There was no scaling. There had been remarkable improvement following roentgen treatment. No further laboratory studies were made at this time.

CASE 4.—An unmarried woman aged 29 came to the clinic on April 13, 1935, because of generalized exfoliative dermatitis, which had begun in the fall of 1932 in the form of dryness and roughness of the palms and fingers. In a few months this condition had extended up the lower part of the arms and legs and by April 1933 had become exfoliative dermatitis. The patient was seen by various physicians and received roentgen treatment. In August 1933 a diagnosis of leukemia of the skin was made by Dr. Oliver S. Ormsby, but in November 1933 biopsy of a lymph node failed to reveal any evidence of a lymphoblastic process. The patient remained under the care of various physicians and received injections of a gold compound, further roentgen treatment and typhoid vaccine. When she was seen by Dr. H. R. Foerster in Milwaukee in April 1934 a diagnosis of lymphatic leukemia was made on the basis of a leukocyte count of 18,500 per cubic millimeter of blood; 59 per cent of the cells were reported as being of the lymphocytic series and 41 per cent as polymorphonuclear leukocytes. Biopsy of tissue from the forearm revealed a lymphoblastomatous picture, but it suggested the possibility of cutaneous Hodgkin's disease more than leukemia. Temporary improvement followed further roentgen treatment in conjunction with the administration of pills containing arsenic trioxide.

Examination at the clinic in April 1935 revealed generalized exfoliative dermatitis, only the skin of the face remaining free. There was a general brownish pigmentation of the skin, and a few more deeply pigmented macules were present, some of which may have been caused by roentgen or arsenic therapy. There were no keratoses on the palms or soles. Definite purpuric spots were present on the buccal mucous membrane and a few also on the trunk. The patient complained of the most intense pruritus. She had lost 15 pounds (6.8 Kg.) in the preceding few months. Studies of the blood revealed the following picture: a predominance of leukocytes with the definite characteristics of reticular cells, being about equally divided between lymphocytes and monocytes; an occasional very immature cell was present which exhibited the features of the reticular cells. A diagnosis was made of reticulo-endotheliosis of the Schilling type. Touch smears from the specimen for biopsy presented a picture identical with that of the blood smears. Biopsy revealed a definite lymphoblastomatous infiltrate in the upper portion of the cutis, containing many grooved monocytes and others showing notched serration of the nuclei. This supported the diagnosis of monocytic leukemia of the Schilling type (leukemic reticulosis). The majority of the cells were larger than those seen in chronic lymphatic leukemia.

The patient returned to Milwaukee and had further roentgen treatment and injections of ethyl chaulmoograte. She then went to her home in Fort Wayne, Ind., from which city Dr. W. W. Duemling wrote us in October 1936 that there had been a gradual increase in the leukocyte count, which then was 170,000 per cubic millimeter, 95 per cent of the cells being of the lymphocytic series. The patient still presented the picture of exfoliative dermatitis, but the lymph nodes were smaller. Her general health remained good. She has had further roentgen treatments and injections of ethyl chaulmoograte as well as arsenic trioxide.

The blood smears which Dr. Duemling forwarded to us revealed the picture of chronic lymphatic leukemia. In addition there were many grooved cells of the reticulum series, in other words, cells presenting all the morphologic features of monocytic cells of the Schilling type. These cells, however, were not as numerous as they were in the smears made when the patient was at the clinic in April 1935.

CASE 5.—The patient, a man aged 68, was first seen at the clinic on Sept. 24, 1935, because of extensive purpura involving the trunk and extremities (fig. 3*B*). He first noticed a number of brownish-purplish spots on his face in April. These were treated with ultraviolet radiation, with good results for ten days. They then recurred and gradually became more extensive. By July the purpura had become generalized, and the patient had become weak. In August he noticed lumps on the sides of his neck and in the axilla and groin. In September he received two transfusions of blood of 500 cc. each. There was no change in his general condition, and he was sent to the clinic for diagnosis of the disorder.

Examination revealed extreme generalized ecchymoses and purpura of the skin, with generalized adenopathy and enlargement of the spleen and liver, the spleen extending 8 cm. below the left costal margin and the liver descending below the right costal margin. A specimen for biopsy was not taken because of the danger that the wound would not heal and because the diagnosis could be, and was, made by means of hemocytologic studies. Otherwise, the general examination, including roentgenographic examination of the skull and femur, revealed no abnormality. Urinalysis did not reveal the presence of arsenic or lead. Examination of the blood revealed more or less acute monocytic leukemia of the Schilling type. Many very immature cells of the reticular type, with intermediate stages to practically mature monocytes, were present, but the predominant cell was immature. It is interesting that indentation of the nucleus was present in the extremely young reticular cells and was not a later development, as in the usual monocyte. There was secondary anemia, with some decrease in the number of blood platelets, but there was nothing special so far as the erythrocyte picture was concerned.

Roentgen treatment was given but without benefit; in fact, a greater degree of anemia developed. A blood transfusion was given. The patient's general condition improved somewhat, the adenopathy grew less marked and he was sent home on October 9. The prognosis was guarded. The patient died on Feb. 22, 1936. No postmortem examination was made.

HEMOCYTOLOGY

The Naegeli type of monocytic leukemia may be definitely distinguished from the Schilling type on the basis of hemocytologic studies.[4] There is a tendency among hematologists to separate monocytic leukemia into two types according to derivation of the predominant cell and also according to the distinguishing morphologic characteristics of this cell (fig. 4).

The Naegeli type of monocytic leukemia has the myeloblast or stem cell as the parent cell, and it has been regarded by some investigators as a form of myelogenous leukemia, because of its tendency to terminate

4. Giffin, H. Z., and Watkins, C. H.: The Distinction Between Splenic Anemia and Subleukemic Splenic Reticulo-Endotheliosis, Am. J. M. Sc. **188**:761-767 (Dec.) 1934.

in that condition. One of us (C. H. W.)[5] had under observation a patient with chronic myelogenous leukemia who, during the last seven months of illness, presented all the features of typical monocytic leukemia of the myeloblastic type. The diagnosis rests on the morphologic characteristic of the parent cell, which in this case is the myeloblast. The myeloblast is a relatively large cell, with the nucleus containing a delicate sievelike arrangement of chromatin. The chromatin is usually granular, but it may be in thin strands and is sharply differentiated from the parachromatin, which stains a faint pink with Wright's stain. The chromatin is usually in the background, so that the parachromatin stands out more clearly and seems to predominate, giving the appearance of a sieve, the so-called sievelike nuclear pattern so characteristic of the myeloblast. Usually several nucleoli are present. The nuclear membrane is delicate but nevertheless distinct. The cytoplasm is usually bluish and may have a moderately mottled appearance, but this is of little importance in distinguishing the cell. During differentiation the nucleoli disappear, the chromatin of the nucleus becomes more prominent and the strands thicken and show a tendency to form the stringlike clumps that are typical of the mature monocyte. The cytoplasm gradually loses the bluish tint and becomes slate gray, which is one of the distinguishing features of the mature monocyte.

The diagnosis of the type of monocytic leukemia is made by the presence in the peripheral blood of the myeloblast and the intermediate forms between it and the mature monocyte. In an occasional case there may be immaturity of other myeloid leukocytes, with only a slight predominance in monocytes. For this reason it is probable that the Naegeli type of monocytic leukemia is a form of myelogenous leukemia and not a distinct entity. As long as there is so little knowledge regarding the physiology of the hematopoietic system and the ultimate function of the monocyte, there will continue to be confusion of the subject, and numerous classifications will be proposed. However, at least for the present, it seems that a diagnosis of a separate entity of monocytic leukemia of the Naegeli type is justified, particularly when the monocyte predominates in the peripheral blood to the practical exclusion of the other myeloid leukocytes.

Monocytic leukemia with the reticular cell (reticulo-endothelial cell) as the parent cell, the so-called monocytic leukemia of Schilling, is morphologically, at least, a distinct entity and may be readily differentiated from the Naegeli type of monocytic leukemia by the predominance during the developmental or differentiative phase of the features of the reticulo-endothelial cell, which are even carried over to a certain extent in the mature monocyte. The free reticular cell is, from the

5. Watkins, C. H.: Unpublished observations.

morphologic standpoint, a distinct cell type. It generally is larger than the ordinary leukocyte and usually has an eccentric nucleus, which may be slightly elongated but which usually is almost spherical and presents an arrangement of chromatin that suggests that a groove runs through the central portion of the nucleus. When Wright's stain has been used the chromatin is blue, is sharply differentiated from the parachromatin and is arranged in fine granular strands. The nuclear membrane is sharply defined and delicate; the whole nucleus has a cleancut appearance. The cytoplasm, on the other hand, is generally abundant and rather grayish blue, with a blotchy appearance. Cytoplasmic protrusions are relatively common, and in certain instances the cytoplasmic portion of the cell may stain poorly. The entire cell has a distinctly delicate and youthful appearance. One or more nucleoli may be present in the nucleus. In comparing this cell with the ordinary myeloblast one notes the marked morphologic differences, as illustrated in figure 4. During the differentiative phase to the mature form of monocyte the nuclear pattern becomes heavier and the chromatin strands thicker, but the tendency to groove seems to remain even into the mature form. The cytoplasmic changes are not marked. There is a tendency for a slate color to predominate, and there may be a blotchy appearance in the cytoplasmic changes, which is apparently produced by differences in staining quality.

REVIEW OF THE LITERATURE

The cutaneous manifestations of various types of monocytic leukemia have been described recently in articles by Mercer,[6] Loveman,[7] Lynch [8] and Wayson and Weidman.[9] Specific involvement of the skin frequently begins by simulating the picture of mycosis fungoides, and necrotic, purpuric and hemorrhagic lesions frequently are encountered. Generalized pustular and even bullous lesions, similar to those seen in the other lymphoblastomas, have been described.[10] An increase in the

6. Mercer, S. T.: The Dermatosis of Monocytic Leukemia, Arch. Dermat. & Syph. **31**:615-635 (May) 1935.

7. Loveman, A. B.: Monocytic Leukemia Cutis: Report of a Case with Biopsy Studies, South. M. J. **29**:357-363 (April) 1936.

8. Lynch, F. W.: Cutaneous Lesions Associated with Monocytic Leukemia and Reticulo-Endotheliosis, Arch. Dermat. & Syph. **34**:775-796 (Nov.) 1936.

9. (*a*) Wayson, J. T., and Weidman, F. D.: Aleukemic Reticulosis: An Additional Member of the So-Called Cutaneous Lymphoblastomas, Arch. Dermat. & Syph. **34**:755-774 (Nov.) 1936. (*b*) Weidman, F. D., and Custer, R. P.: The Scope of the So-Called "Cutaneous Lymphoblastomas" in Relation to Lesions of the Haematopoietic System, in Deliberationes Congressus Dermatologorum Internationalis, IX, Budapest, L. Nekam, 1935, vol. 2.

10. Goeckerman and Montgomery.[1] Barney.[2] Lynch.[8]

number of monocytes is frequently seen in a Kaposi sarcoma,[10a] which may at times be associated with the lymphoblastomas.[11] The interrelationship between the various types of lymphoblastoma has been emphasized by many authors,[12] and Fraser and Schwartz [13] have noted especially the prominent rôle that the reticulo-endothelial system of the skin plays in the various lymphoblastomas.

COMMENT

Our cases illustrate most of the various cutaneous manifestations of monocytic leukemia. Case 1, of the Naegeli type, was significant in that the patient was under observation and thorough studies of the blood were made over a period of four years. The condition at first had the clinical features of mycosis fungoides and then of a fairly generalized erythroderma, and later somewhat necrotic nodules developed; yet until the terminal stages of the disease the process apparently remained confined to the skin. There were no changes in the blood or any involvement of the internal organs until shortly before death. Biopsy of the skin was at no time diagnostic as to the type of lymphoblastoma but consistently showed activity of the reticulo-endothelial system, including an increase in *Gitterfasern* and in mature monocytes. It is unfortunate that no microscopic examination of a cutaneous lesion was made just before death or post mortem, as a more specific histopathologic picture might have been encountered. This case represents, we believe, an example of the autochthonous cutaneous origin of monocytic leukemia of the Naegeli type.

Case 3, in contrast, is an example of the Schilling type of monocytic leukemia of autochthonous origin. Beginning with cutaneous lesions resembling mycosis fungoides, as in Weidman's [9] case, the condition later resolved into an exfoliative dermatitis. A peculiar type of grooved and serrated immature monocytic cell could be definitely recognized, both in the second biopsy specimen of the skin and in later blood smears; in retrospect, a few grooved cells were observed in the first specimen of skin taken for biopsy a year previously. This, we believe, is the first case of exfoliative dermatitis to be reported as due to monocytic leuke-

10a. Dörffel, Julius: Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, Arch. Dermat. & Syph. **26**:608-634 (Oct.) 1932.

11. Lane, C. G., and Greenwood, A. M.: Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, Arch. Dermat. & Syph. **27**:643-657 (April) 1933.

12. Loveman, A. B.: Cutaneous Manifestations of the Lymphoblastomas: Report of a Case of Hodgkin's Disease, J. A. M. A. **104**:1583-1586 (May 4) 1935. Wayson and Weidman.[9a] Goeckerman and Montgomery.[1]

13. Fraser, J. F., and Schwartz, H. J.: Neoplastic Disease of the Reticulo-Endothelial System, Arch. Dermat. & Syph. **33**:1-10 (Jan.) 1936.

mia (Schilling). In both cases 1 and 3 the early histopathologic picture of the skin closely resembled that of mycosis fungoides. We are familiar with the increase in *Gitterfasern* and the increase in monocytes in mycosis fungoides.[13] This condition may persist as such or terminate as lymphosarcoma, especially of the reticulum cell type, or it may even terminate as any of the other lymphoblastomas. It is not surprising, therefore, to find the Naegeli and Schilling types of monocytic leukemia falling into this group. In case 4 the cutaneous changes were recognized first, and negative results of biopsy of a lymph node speak against the systemic origin of the condition. A hemocytologic picture of lymphatic leukemia was encountered at the time biopsy of the skin showed lymphoblastoma and suggested the presence of Hodgkin's disease. Later, both biopsy and the hemocytologic picture revealed monocytic leukemia (Schilling), when an exfoliative dermatitis was present clinically. Recent blood smears showed more the picture of lymphatic leukemia. This case again emphasizes the interrelationship of the lymphoblastomas.

Case 2 was a case of typical monocytic leukemia of the Naegeli type in which, in the terminal phase, discrete specific nodules were present in the skin, such as are frequently noted in leukemia cutis, especially of the lymphatic type, and rarely in myelogenous leukemia. There was nothing characteristic in the clinical appearance of these nodules.

Case 5 revealed generalized and the most severe purpuric and hemorrhagic lesions we have ever seen and justly emphasizes, as has been brought out by Lynch [8] especially, that purpuric lesions are often encountered in monocytic leukemia of the Schilling type. A few such lesions were present in case 4. Purpuric and necrotic cutaneous lesions are not an uncommon finding in any of the lymphoblastomas, especially in the terminal phases of the disease. Unfortunately, no specimen for biopsy was taken in case 5, so we do not know whether the cutaneous lesions were simply toxic or represented true specific infiltration of the skin.

TREATMENT

It has been the experience of one of us (C. H. W.) that monocytic leukemia of the Schilling type is a more benign form than the Naegeli type, although of course it eventually proves fatal. It seems that high voltage roentgen or radium therapy is indicated if the process is not too acute, but the dose should be given with careful observation of the hematologic changes, in order to determine the resistance of the cells to treatment. The cutaneous lesions frequently show a striking though temporary involution after superficial local roentgen therapy, although involution of all lesions also may result after systemic high voltage roentgen therapy, including lesions in areas of the skin not

treated. Local applications, in an attempt to control the pruritus or secondary infection, and arsenic and fever therapy also may be of temporary value.

SUMMARY AND CONCLUSIONS

Distinction is made between monocytic leukemia of the Naegeli and that of the Schilling type on the basis of the hemocytologic pictures. Either type may be of primary autochthonous cutaneous origin. The type of cutaneous manifestations of either condition may be specific or nonspecific and may vary from discrete necrotic nodules or purpuric lesions to generalized exfoliative dermatitis. A distinctive histopathologic picture of monocytic leukemia of the Schilling type may be observed on examination of the skin, corresponding to the hemocytologic picture. Occasionally, myelogenous leukemia may terminate as monocytic leukemia of the Naegeli type,[5] or, as in case 4, lymphatic leukemia may result in monocytic leukemia (Schilling) and still later again present the blood pictures of both conditions. Monocytic leukemia of the Schilling type (leukemic reticulo-endotheliosis) may assume an acute or chronic form, and even aleukemic reticulosis may be encountered.[9a]

It is important, therefore, to correlate the cutaneous as well as the general clinical, pathologic and hemocytologic observations in a given case in order to arrive at a correct diagnosis. A prolonged period of observation may be necessary before it is possible to ascertain the type of lymphoblastoma that will eventuate.

ALTERATIONS IN SERUM PROTEIN AS AN INDEX OF HEPATIC FAILURE

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For some time we have been interested in the changes in the protein content of the serum in hepatic disease. The basis of this interest lies in numerous clinical and experimental observations. Whipple [1] found that the liver produces fibrinogen. Less conclusively other experiments have indicated that the liver is the site of formation of the albumin of serum. Clinical observations and studies show that there are changes in the protein content of the blood in hepatic disease. This fact was first observed by Grenet [2] and Gilbert [3] in 1907, who found a diminution of the total protein content of the blood in cases of cirrhosis of the liver. Filinski [4] described cases of cirrhosis in which the total protein content was decreased, chiefly in the albumin fraction, with some elevation of the globulin content. His observation, confirmed by Abrami and Wallich,[5] have received repeated verification in the literature recently reviewed by Myers and Keefer [6] and Snell.[7] Serum protein

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1. Whipple, G. H.: Fibrinogen: An Investigation Concerning Its Origin and Distribution in the Body, Am. J. Physiol. **33**:50 (Jan.) 1914.

2. Grenet, H.: Diminution des albumines du sérum sanguin chez les hépatiques, Compt. rend. Soc. de biol. **63**:552, 1907.

3. Gilbert, A., and Chiray, M.: Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, Compt. rend. Soc. de biol. **63**:487, 1907.

4. Filinski, W.: L'augmentation de taux de la globuline dans le sérum du sang, Presse méd. **20**:236 (March 18) 1922.

5. Abrami, P., and Wallich, R.: Modifications du sérum sanguin au cours des cirrhoses du foie avec ascites: Inversion du rapport sérums-globulines, Compt. rend. Soc. de biol. **101**:291 (May 31) 1929.

6. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, Arch. Int. Med. **55**:349 (March) 1935.

7. Snell, A. M.: Changes in Proteins of Blood in Hepatic Disease, Proc. Staff Meet., Mayo Clin. **10**:489 (July 31) 1935.

has been studied in forms of hepatic damage other than cirrhosis and has been found to be altered roughly in proportion to the severity of the damage (Myers and Keefer [6]).

Experimentally there have been extensive studies of the blood protein in animals under various conditions affecting the liver, particularly necrosis after the administration of chloroform and phosphorus and after ligation of the common duct, the production of an Eck fistula and hepatectomy. Beginning with the studies of Kerr, Hurwitz and Whipple,[8] experimental attempts have been made to determine the rôle of the liver in protein metabolism. Whipple and his associates showed that depletion of the protein content of the serum by plasmapheresis is followed by a regeneration of the protein and that globulin is replaced more rapidly than albumin. The regeneration of the protein was delayed in animals in which the liver was damaged by phosphorus or chloroform before depletion of the plasma. These workers attributed part of the slow regeneration of protein to the low intake of food associated with hepatic injury and consequent intoxication. Henriques and Klausen [9] recorded a decrease in the albumin but not in the globulin content of the plasma in rabbits after phosphorus poisoning. Sawada [10] found a decrease in the albumin content and a slight elevation of the globulin content in animals with hepatic damage from phosphorus, chloroform and tetrachloride poisoning and also from inoculation with Schistosomum japonicum.

In the hepatic damage following ligation of the common bile duct Henriques and Klausen,[9] Sawada,[10] Bollman [11] and Foley and his associates [12] found a decrease of the albumin content with an increase of globulin occurring from one to three months after the ligation. Pertinent is the criticism of Whipple and his associates [8] that under the influence of obstructive jaundice there is a marked disinclination on the part of the animal to eat; and because of this, the inadequate supply

8. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Proteins: I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion, Am. J. Physiol. **47**:356, 1918; II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, ibid. **47**:370, 1918; III. Liver Injury Alone: Liver Injury and Plasma Depletion; the Eck Fistula Combined with Plasma Depletion, ibid. **47**:379, 1918.

9. Henriques, V., and Klausen, U.: Untersuchungen über den Serumalbumin- und Serumglobulingehalt des Serums unter wechselnden Umständen, Biochem. Ztschr. **254**:414, 1932.

10. Sawada, T.: Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, Jap. J. Gastroenterol. **3**:38, 1931.

11. Bollman, J. L.: Influence of Diet in the Experimental Production of Ascites, Proc. Staff Meet., Mayo Clin. **3**:137, 1928.

12. Foley, E. F.; Keeton, R. W.; Kendrick, A., and Darling, D.: Serum Protein Studies Following Ligation of the Common Bile Duct, to be published.

of protein contributes to the low values for albumin. Diet was not mentioned by Henriques and Klausen or by Sawada. In the studies quoted by Bollman [13] milk, a complete protein, was the chief constituent of the diet. Foley and his colleagues [12] found that control animals, which had not been operated on and which were fed the same diet as the dogs that had been operated on (milk, cream, eggs, butter, cheese and bread), did not show alterations in the protein content of the serum. Dogs with Eck fistulas (Whipple [8]) show a distinct inability to regenerate the protein of the blood after depletion of the plasma. Jürgens and Gebhardt,[14] working with dogs with Eck fistulas, found that an increase in globulin developed two or three weeks after the operation. Meat feeding depressed the albumin value and raised the globulin value, while carbohydrate feeding reversed this phenomenon in the normal direction. In hepatectomized animals Mann and Magath [15] found a decrease in the total protein content and a decrease in the albumin and globulin values, with a tendency for the reversal of the albumin-globulin ratio. Similar results were obtained by Cantô.[16] By diet alone Holman, Mahoney and Whipple [17] were able to produce alterations in the protein similar to those which have previously been mentioned as being associated with disorders of the liver. This diet, however, contained no animal and a minimal amount of vegetable protein. On this diet low in protein some dogs maintained a normal value for protein for seven weeks, while others showed a reversal of the albumin-globulin ratio after two months. Weech, Snelling and Goettsch [18] described a diet supplying an inadequate intake of protein on which dogs showed a progressive decrease of the protein (albumin) content of the serum and a constant level for globulin, with the subsequent development of edema and ascites. In approximately twenty experiments the decrease in the total protein (albumin) content of the serum was 1 Gm. per hundred cubic centi-

13. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies of the Physiology of the Liver, Am. J. Physiol. **78**:258, 1926.

14. Jürgens, R., and Gebhardt, F.: Ueber die Eiweisskörper des Blutes bei experimenteller Leberschädigung durch die Eck-Fistel, Arch. f. exper. Path. u. Pharmakol. **174**:532, 1934.

15. Mann, F. C., and Magath, T. B.: Die Wirkungen der totalen Leberexstirpation, Ergebn. d. Physiol. **23**:212, 1924.

16. Cantô, A.: Variations des protéines du plasma sanguin aprés l'hépatectomie, Compt. rend. Soc. de biol. **104**:1103, 1930.

17. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Controlled by Diet: I. Liver and Casein as Potent Diet Factors, J. Exper. Med. **59**:251 (March) 1934.

18. Weech, A. A.; Snelling, C. E., and Goettsch, E.: The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, J. Clin. Investigation **12**:217, 1933.

meters. The evidence may be summarized in the quotation of Kerr, Hurwitz and Whipple:[8] "All this experimental evidence points to the liver as concerned in maintaining the normal level of the serum proteins."

Since alterations of the protein may occur in the presence of hepatic disease, we wished to determine the diagnostic and prognostic value of such alterations. A study of patients with cirrhosis of the liver, compensated and decompensated, and others with intrahepatic and extrahepatic jaundice was made. The control groups included patients with ascites without clinical cirrhosis and patients on severely deficient diets in whom there was no evidence of hepatic disease. These groups were sufficiently diversified to permit a study of chronic, advanced, diffuse hepatic damage as well as varying degrees of less extensive damage. We were able to observe to some extent the relation of the intake of food to the alteration of the protein content of the serum.

METHODS

About 15 cc. of blood was drawn from the cubital vein while the patient was in a fasting state. After clotting had occurred the serum was drawn off with a pipet. Quantitative determinations of the protein were made according to the gasometric method of Van Slyke.[19] For a group of healthy males and females our results compare favorably with the normal values given by Peters and Van Slyke.[20]

RESULTS

A. Cirrhosis of the Liver with Ascites.—There were twenty-one patients with cirrhosis of the liver with ascites (table 1), seventeen of whom presented the classic picture of advanced portal cirrhosis with marked ascites. There were two patients with cardiac cirrhosis in whom evidences of hepatic damage persisted after cardiac compensation had been established. With the exception of three patients, none showed albumin in the urine. In two of these the quantity was insignificant. In no instance was paracentesis performed before the protein of the serum was measured. This precluded the loss of proteins by mechanical removal. The results are practically identical with those obtained by Filinski[4] and others, in that a decrease in the albumin content and an elevation of the globulin content with a reversal of the albumin-globulin ratio were noted. In four instances the total protein content was normal, but in these the high values for total protein were due to an increase in the globulin content (5 Gm. or more per hundred cubic centimeters).

19. Peters, J., and Van Slyke, D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932.

20. Peters, J., and Van Slyke, D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, Williams & Wilkins Company, 1932.

TABLE 1.—*Cirrhosis with Ascites*

Patient No.	Patient Name	Blood: Protein, Gm. per 100 Cc. Total	Albumin	Globulin	Albumin-Globulin Ratio	Nonprotein Nitrogen, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	Icteric Index	Albumin in Urine	Dye Test*	Size of Spleen	Survival After Determination, Days	Type of Cirrhosis: Clinical Diagnosis	Postmortem Diagnosis
1	J. M.	7.84	2.38	5.46	0.40	30.0	10.0	3.98	125	+	—	+	5	.....	Atrophic acute yellow necrosis
2	J. W.	7.56	1.86	5.70	0.32	26.4	11.0	4.36	40	0	60	+	13	Atrophic	
3	S. K.	6.10	2.42	3.68	0.65	23.2	7.0	2.70	15	0	—	+	14	Atrophic	Atrophic
4	J. B.	5.42	1.53	3.89	0.37	31.0	8.8	2.80	30	0	40	+	15	Atrophic	
5	F. B.	4.89	1.64	3.25	0.50	32.3	9.8	3.10	22	0	—	+	18	Atrophic	
6	W. M.	5.98	2.18	3.80	0.77	17.0	8.0	3.20	75	0	40	+	21	.....	Atrophic
7	M. N.	5.96	1.77	4.19	0.42	26.0	10.0	3.20	28	0	—	+	27	Atrophic	
8	C. D.	6.95	1.95	5.00	0.39	24.3	10.0	3.09	18	Trace	45	+	31	.....	Atrophic
9	C. H.	6.29	1.38	4.91	0.29	21.5	10.0	3.40	18	0	—	+	36	.....	Atrophic
10	J. Z.	5.34	2.42	2.92	0.89	43 0	11.0	3.80	12	0	30	+	43	.....	Atrophic
11	J. S.	5.47	2.04	3.43	0.59	42 3	8.0	3.48	14	0	35	+	49	.....	Atrophic
12	J. K.	7.90	2.36	5.54	0.40	24.0	9.0	2.20	17	0	40	+	56	Atrophic*	
13	M. G.	6.06	2.30	3.76	0.61	24 0	7.0	2.60	25	0	25	+	60	.....	Atrophic
14	J. K.	4.14	1.83	2.31	0.79	19.2	8 0	2.60	22	0	50	+	70	Alcoholic	
15	J. H.	6.14	3.08	3.06	1.00	26.2	14.0	4.60	8	0	20	+	75	Alcoholic	
16	S.	7.87	1.75	6.12	0.28	41.0	15.0	4.27	12	0	30	0	77	Alcoholic	
17	P. B.	6.38	1.27	5.11	0.25	26.8	10.0	3.15	12	0	40	+	..	Amyloid	
18	M. N.	6.91	3.02	3.89	0.76	19.6	9.6	3.10	102	+	50	0	..	Alcoholic	
19	E. B.	6.71	2.97	3.74	0.80	28.6	9.0	3.52	72	0	60	+	..	Obstructive biliary	
20	D. K.	5.63	2.57	3.06	0.84	42.0	16.0	4.47	11	+++	20	+	—	Cardiac	
21	J. M.	4.70	2.07	2.63	0.79	23.7	13 2	4.40	14	0	—	+	—	Cardiac	

* Percentage of bromsulphalein retained at the end of thirty minutes.

TABLE 2.—*Decompensated Cirrhosis with Subsequent Compensation*

	Blood: Protein, Gm. per 100 Cc. Total Protein	Albumin	Globulin	Albumin-Globulin Ratio	Nonprotein Nitrogen, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	Icteric Index	Albumin in Urine	Dye Test	Size of Spleen	Comments
12/ 3/34	6.60	1.86	4.74	0.40	21.98	4.7	2.85	42	0	35	+	Ascites present; 500 cc. of blood given 12/10 and 12/17
12/18/34	6.78	3.27	3.51	0.90	18.97	8.7	3.50	24	0	—	+	500 cc. of blood given 12/28
1/ 2/35	7.28	3.44	3.84	0.89	23.10	8.5	3.70	14	0	—	+	500 cc. of blood given 1/9/35; no ascites
6/16/35	7.57	4.31	3.26	1.30	22.80	11.5	4.20	12	0	15	+	No ascites
1/18/36	7.94	4.87	3.07	1.60	.....	12.0	4.50	12	..	—	+	No ascites; liver greatly enlarged

The data are arranged in the order of duration of life (expressed in days) after the determinations were made. The seventeen patients with portal cirrhosis showed an average duration of life of forty-four days, with a minimum of five and a maximum of seventy-seven days. These results merely affirm the clinically recognized fact that ascites (a symptom indicating portal decompensation) in cirrhosis is an unfavorable prognostic sign. It is suggested that these striking changes in the protein of the blood represent a failure of the proteogenic function of the liver and therefore a serious impairment of a vital metabolic process.

The Decrease in Albumin Is Not Due to Mechanical Removal: In table 2 are presented the results obtained for a patient with the hypertrophic form of alcoholic cirrhosis during decompensation and subsequent compensation. A year previously this patient had been in the hospital with jaundice and ascites which had developed after a period of alcoholic excesses. These symptoms disappeared after the patient had spent two months in the hospital, but at the time of his discharge the spleen and liver were markedly enlarged. In December 1934 he returned to the hospital with jaundice and ascites, which again had developed after an alcoholic episode. During the period of portal decompensation the usual changes in the protein occurring in hepatic failure were observed. Four transfusions of whole blood were given at weekly intervals, in addition to large amounts of carbohydrate. After the second transfusion the value for albumin practically doubled. Improvement continued, with the complete disappearance of both jaundice and ascites after the fourth transfusion. After compensation the protein assumed a normal direction but not a normal level. Determinations made six months and one year later showed a high level for globulin but a practically normal level for albumin. It seems that during the acute exacerbation of the hepatic disturbance this patient was unable to maintain his stores of protein, but he has since beeen able to supply adequate quantities of protein after its restoration through blood transfusion and reabsorption of the ascitic fluid.

In table 3 are listed the data for patients with ascites without clinical cirrhosis of the liver. In this group were five patients with ascites due to carcinoma, with metastasis either to the liver or to the peritoneum. Paracentesis had been performed twice on one patient prior to his admission to the hospital but not on the others. Although the loss of protein in the ascitic fluid is comparable to that which occurs in cirrhosis prior to paracentesis, similar changes did not occur in the protein of the serum. Likewise in the patients with ascites due to tuberculous peritonitis and congestive heart failure, the protein of the serum behaved in a normal manner. These instances indicate that there may be a transudation of protein into larger accumulations of ascitic fluids with-

TABLE 3.—*Ascites Without Clinical Cirrhosis of the Liver*

Patient		Blood											Diagnosis	
		Protein, Gm. per 100 Cc.				Non-protein Nitrogen, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	Icteric Index	Albumin in Urine	Dye Test	Size of Spleen		
No.	Name	Total	Albumin	Globulin	Albumin-Globulin Ratio								Autopsy	Clinical
1	A. R.	7.29	3.99	3.30	1.20	30.0	9.5	4.00	9	0	—	0	Carcinoma of tail of pancreas; metastases to liver	
2	J. O.	6.65	3.51	3.14	1.10	46.0	11.0	4.20	21	0	10	0	Myxoma peritonei	Myxomatous carcinoma of appendix with metastases to peritoneum
3	E. M.	7.02	3.50	3.52	1.00	30.0	13.0	4.40	7	0	10	0	Carcinoma of peritoneum; nutmeg liver	
4	C. S.	5.12	3.07	2.05	1.50	61.0	8.4	2.75	39	0	10	0	Carcinoma of stomach; metastases to liver	
5	J. C.	7.53	4.52	3.01	1.50	30.0	9.9	4.95	100	0	100	0		Carcinoma of extrahepatic bile passages
6	A. R.	7.63	4.23	3.40	1.19	30.3	10.0	4.11	8	0	—	0		Tuberculous peritonitis
7	M. M.	6.53	4.40	2.13	2.60	34.9	12.0	4.85	10	0	—	0		Congestive heart failure
8	F. H.	5.28	3.47	1.81	1.90	26.0	11.0	4.40	11	Trace	10	0		Congestive heart failure

out alterations of the serum protein. As was mentioned previously, in our patients with cirrhosis paracentesis had not been performed prior to the determinations of the protein, so that the amount of protein lost was represented by that quantity which had passed into the accumulated ascitic fluid. By contrast, the results obtained in another case (table 3, patient 2) are especially important. Clinically this patient presented marked ascites, for the relief of which paracentesis was frequently performed. Over a period of one hundred and eighty days there was removed from the abdomen approximately 59,200 cc. of a thick, mucilaginous fluid, analysis of which yielded 5.47 Gm. of total protein per hundred cubic centimeters of fluid (albumin, 2.16 Gm.; globulin, 3.31 Gm.). During this time the total estimated loss of protein, exclusive of the initial amount, was 2,445 Gm., or a daily loss of 13.5 Gm. The protein content of this fluid was practically the same as that of blood, so that at each paracentesis the experimental conditions of plasmapheresis were duplicated. The determinations on the blood made at the time of the final paracentesis (total protein, 6.97 Gm.; albumin, 3.43 Gm.; globulin, 3.54 Gm.) showed a negligible fall in the amount of protein as compared with the quantity present in the serum (total protein, 6.65 Gm.; albumin, 3.51 Gm.; globulin, 3.14 Gm.) six weeks prior to the initial tapping. At autopsy the liver grossly was normal in size and appearance, but the visceral and the parietal peritoneum were studded with biscuit-sized carcinomatous nodules which had their origin in a myxomatous carcinoma of the appendix. This patient then represents an instance of the extreme loss of protein into the ascitic fluid in the presence of a normal liver. In spite of the repeated removal of fluid, there was no depletion of the serum albumin, such as occurred in the patients with cirrhosis of the liver from whom the ascitic fluid had not been removed. This case corroborates the experience of others in demonstrating that the loss of protein into the ascitic fluid is per se not the cause of the depletion of the serum albumin. This question of the loss of albumin in the ascitic fluid and its relation to hypo-albuminemia has recently been discussed by Myers and Keefer.[6] They cited cases of cirrhosis in which repeated paracentesis, with the loss of as much as 18 Gm. of protein per day in the ascitic fluid, did not lead to a progressive decline in the level of the blood protein. They pointed out that this amount of protein lost daily can be regenerated in experimental animals undergoing plasmapheresis. They concluded that loss of the protein in the ascitic fluid is not adequate explanation of the low levels of protein in the blood.

The Decrease in Albumin Is Not Due to an Inadequate Intake of Protein: Five patients were studied who showed no clinical evidences of hepatic damage, but there were marked dietary restrictions. The first

patient was a young woman who, because of a psychasthenic reaction, voluntarily reduced her intake of food so that she lost 16 pounds (7 Kg.), her weight being reduced from 118 to 72 pounds (53.5 to 33 Kg.) in from twelve to fourteen weeks. The emaciation was extreme, and polyneuritis was so severe that she could only shrug her shoulders. She had to be turned in bed by nurses and fed for ten days with a nasal catheter. The second case was that of a woman with chronic intestinal obstruction. There was protracted vomiting for eight weeks, little food being retained, except for brief intervals during which liquids were administered through a duodenal tube. Water and salt were given parenterally. The third case was that of a man who had been living on scraps of food salvaged from garbage cans. He was found in an exhausted state on the street and showed severe scurvy with extensive hemorrhages and marked anemia. While his intake of protein was not known, it was deficient. There were two patients with malignant growths, one having sarcoma of the bone and the other having carcinoma of the lung. Both patients showed marked anorexia and emaciation. In all these cases [21] there was some decrease in the total protein content of the serum but no elevation of the globulin content. The albumin-globulin ratio remained normal. It has frequently been pointed out that globulin is regenerated more readily than albumin. Although exact quantitative estimations of the intake of food of the patients with cirrhosis are not given, it is known that they (table 1) ate ward diet satisfactorily and hence must have obtained more protein than the control patients mentioned previously. In this connection the metabolic experiments of Liu and his colleagues [22] are important. Their studies of human beings in whom nutritional edema had developed as the result of starvation indicated the presence of a depletion of the protein of the plasma, with a reversal of the albumin-globulin ratio. The addition of 28 Gm. of protein to the daily ration reestablished the normal level of the protein. From this experience it seems that a small intake of protein is adequate to prevent the fall of the protein content of the plasma when there is no deficiency in synthesis. In nephrosis there is no evidence of alteration of hepatic function or of its capacity to regenerate protein. In this condition it has been shown by Barker and Kirk [23] that the daily loss of protein in the urine is from 5 to 60 Gm. and that a loss of 4 Gm. a day is associated with a fall in the protein level of the serum. This drop is attributed to the loss in the urine. The loss affects chiefly the

21. The tabulated detailed data for these patients are omitted to conserve space.

22. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Nutritional Edema, Chinese J. Physiol. **6**:73, 1932.

23. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

albumin factor and progresses to a reversal of the albumin-globulin ratio. They further stated that patients losing less than 10 Gm. of albumin per day show a "remarkable benefit from a high protein diet," which restores the protein of the serum. In the presence of diffuse hepatic damage an adequate or high protein diet does not maintain or reestablish the protein content of the blood, because of the impairment of the proteogenic function. Further evidence that the change in the protein is not the result of protein deprivation is illustrated by patient 1 (table 1). This middle-aged man had an adequate intake of food until the onset of hepatic necrosis. One week before entrance to the hospital he had taken some unknown drug to induce sleep. On entrance marked jaundice and some ascites were noted. Determinations of the protein content of the serum were made on his second day in the hospital, or eight days after the onset of illness. Although he was able to partake of the ward diet, which contained 60 Gm. of protein daily, the albumin content had dropped to 2.36 Gm., and the globulin content had risen to 5.46 Gm. There followed progressive jaundice, cholemia, hemorrhagic diathesis and death five days later. Autopsy revealed a small liver with extensive necrosis of the parenchyma. The history, obtained from the patient's wife, did not indicate dietary restriction prior to his entrance. Similar alterations of the protein content of the serum were recorded by Longcope [24] in acute yellow atrophy of the liver.

The Decrease in Albumin in Patients with Hepatic Damage Persists in Spite of an Increased Intake of Protein: The history of patient 9 (table 1) is significant. This patient had typical cirrhosis of the liver with marked ascites. He consumed at our suggestion 120 Gm. of liver daily, because the experiments of Holman, Mahoney and Whipple [17] showed the efficiency of liver in regeneration of plasma protein after plasmapheresis. The clinical progress of the disease seemed to be more rapidly downward than usual. At the time of the first determination of the protein content of the serum he was an ambulatory outpatient, yet the progress of his illness was such that death occurred thirty-six days later. One wonders whether the rapid deterioration could not be ascribed to the liver diet. This would be in keeping with the results of Bollman,[11] who noted that the addition of meat to the diet of dogs with ligated common ducts regularly produced ascites and symptoms similar to "meat intoxication" occurring in dogs with Eck fistulas. A similar study was made of another patient with cirrhosis of the liver on a liver diet, but records of the protein content of the blood are not available. Such data indicate that in cirrhosis the addition to the diet of adequate protein ("building stones") may not favorably influence

24. Longcope, W. T.: The Importance of Disturbances in Nutrition in Edematous States, New England J. Med. **210**:1243, 1934.

the regeneration of protein. They suggest also that the damaged liver not only loses its capacity to synthesize serum protein but may lose also its ability to protect the body from toxic effects of ingested proteins.

B. Other Forms of Hepatic Damage.—In cases of hepatic disease manifested by jaundice without ascites (table 4) there may be either extrahepatic obstruction or intrahepatic destruction. There were eleven patients with extrahepatic obstruction for whom the diagnosis was established by operation or autopsy. Among these were three patients with stone in the common duct (patients 1 to 3) with marked reversal of the albumin-globulin ratio. All three died in spite of adequate preoperative management, conservative surgical measures and careful postoperative care, including transfusions, infusions of dextrose and buffer solution, duodenal siphonage and the administration of decholin. In contrast, two patients with calculous cholecystitis (patients 4 and 5) with normal values for protein made an uneventful postoperative recovery. In five patients with malignant extrahepatic obstruction with jaundice, less marked alteration of the protein occurred. In the group of patients with intrahepatic jaundice the results of the studies of the serum protein paralleled the clinical course. Three patients with pneumonia (patients 12 to 14) showed a reversal and death. Two of these were jaundiced. One other patient with pneumonia (not jaundiced) showed no reversal and recovered. Five patients with "catarrhal jaundice" (patients 16 to 20) showed no reversal and the usual recovery. One patient with chronic low grade jaundice,[22] a young woman whose employment required the use of benzene, showed no reversal. This patient's clinical condition remained unchanged after one year of observation. There was one young alcoholic patient with delirium tremens and jaundice [23] who had complete recovery. There was no reversal, even though there had been dietary restriction.

C. Application of This Principle in Diagnosis of Hepatosplenomegaly.—There were four patients with hepatosplenomegaly for whom studies of the protein content of the serum were of diagnostic value.[21] In one of these, while the total protein content was close to the level for edema, there was no alteration of the globulin content. A diagnosis of cirrhosis of the liver was eliminated on this basis. Autopsy revealed Hodgkin's disease. In one of the others there was an elevated globulin content with a slight decrease in the albumin content and a reversal of the ratio. This patient had a clinical history of untreated syphilis, with positive serologic tests. Elevation of the globulin content of the serum has been observed in syphilis by Noguchi.[25] Hence a diagnosis of syphilis of the liver which had not reached the stage of decompensated cirrhosis

25. Noguchi, H.: The Relation of Protein Lipoids and Salts to the Wassermann Reaction, J. Exper. Med. **11**:84, 1909.

TABLE 4.—*Other Forms of Hepatic Damage Without Ascites*

Patient		Blood										Diagnosis	
		Protein, Gm. per 100 Cc.				Non-protein Nitrogen, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	Icteric Index	Albumin in Urine	Dye Test	Size of Spleen		
No.	Name	Total	Albumin	Globulin	Albumin-Globulin Ratio								Clinical	Autopsy
1	E. S.	7.27	2.94	4.33	0.68	24.0	13.0	4.80	44 to 115	+	30	0	Stone in common duct; operation	Not obtained
2	J. D.	5.63	2.78	2.85	0.90	27.1	13.0	3.80	165	0	100	0	Stone in common duct	Biliary cirrhosis
3	G. S.	5.88	1.47	4.43	0.30	49.5	10.0	3.10	74	0	—	0	Stone in common duct; suppurative cholecystitis	Death
4	W. P.	6.65	3.46	3.19	1.08	30.0	12.0	4.20	37	0	—	0	Calculous cholecystitis; stone in cystic duct; operation	Recovery
5	B. H.	8.28	5.16	3.12	1.60	30.0	12.4	3.15	16	0	0	0	Calculous cholecystitis	Recovery
6	S. C.	7.53	4.52	3.01	1.15	30.0	9.9	4.90	160	0	90	0	Carcinoma of extrahepatic bile passages	
7	E. S.	6.96	3.50	3.46	1.00	30.0	9.5	2.40	107	0	80	0		Carcinoma of common bile duct
8	S. L.	6.43	3.17	3.26	0.90	28.8	16.0	5.30	134	0	60	0		Carcinoma of hepatic duct
9	G. R.	6.92	3.91	3.01	1.30	53.0	14.0	4.80	34	0	—	0	Carcinoma of extrahepatic ducts; operation	
10	J. F.	6.48	3.57	2.91	1.20	18.0	10.0	3.10	150	0	45	+		Carcinoma of common bile duct
11	J. R.	7.57	4.23	3.34	1.27	26.0	10.0	3.50	75	0	—	0		Carcinoma of head of pancreas
12	G. M.	5.64	1.86	3.78	0.46	30.0	10.5	3.20	40	Sugar +	—	—	Lobar pneumonia; cirrhosis	
13	S. H.	5.74	2.80	2.94	0.90	113.9	15.0	4.80	90	+	—	0		Lobar pneumonia; hepatitis
14	A. K.	4.40	1.83	2.57	0.71	74.9	15.0	4.80	18	Trace	—	0	Pneumonia	
15	E. W.	6.15	3.74	2.41	1.10	21.9	11.0	4.40	12	+	35	0	Catarrhal jaundice	
16	J. F.	6.90	4.20	2.70	1.50	30.0	14.0	4.60	55	0	—	+	Catarrhal jaundice	
17	N. C.	5.50	3.56	1.94	1.80	21.4	13.5	4.20	120	0	—	+	Catarrhal jaundice	
18	S. M.	6.74	4.60	2.14	2.15	22.6	15.0	4.60	95	0	—	0	Catarrhal jaundice	
19	E. N.	7.37	4.65	2.72	1.70	25.0	15.5	5.20	95-12	0	50	+	Catarrhal jaundice	
20	J. B.	6.54	3.71	2.05	1.80	61.0	15.0	5.10	125	0	80	+	Catarrhal jaundice	
21	E. W.	5.83	3.13	2.73	1.10	20.5	12.5	4.30	29	0	60	0	Chronic hepatitis	
22	J. B.	5.48	3.19	2.29	1.30	22.9	13.0	4.80	32	+	30	0	Delirium tremens; alcoholic hepatitis	

was made. While two other patients presented the clinical history of alcoholic cirrhosis, studies of the blood protein showed a normal value for albumin, with a slight increase in the globulin content. The diagnosis was the hypertrophic form of compensated cirrhosis of the liver with adequate hepatic function.

SUMMARY AND CONCLUSIONS

In the literature there is abundant evidence that the liver plays an important rôle in the synthesis of serum albumin.

In decompensated portal cirrhosis there is a low value for serum albumin, with elevation of the globulin content and a reversal of the albumin-globulin ratio.

Evidence is offered that this alteration in the protein is not due to mechanical loss in ascitic fluid or restriction of the intake of protein and that it is not abolished by an increased protein content.

The alterations in the protein are attributed to hepatic damage and to the loss of the liver's ability to synthesize serum albumin.

In some cases the damage becomes so severe that an adequate intake of protein may lead to a more rapid progress of the disease. In such cases the liver has apparently lost its ability to detoxify protein metabolites.

In other forms of hepatic disease there is parallelism between the extent of hepatic damage and the alterations of the serum protein.

The determination of serum protein is often a helpful procedure in the diagnosis of obscure conditions in which there is hepatosplenomegaly.

ACUTE URANIUM NEPHROSIS

THE MECHANISM OF THE GLYCOSURIA

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Although the experimental nephrosis induced by uranium nitrate has been studied extensively, many of the factors influencing the excretion of urinary substances in this condition are still imperfectly understood.

The present investigation was undertaken originally to demonstrate more clearly the mechanism of the glycosuria which occurs during the early stages of the nephrosis induced by uranium. Later the studies were extended to urinary substances other than sugar, and the output of nitrogen, chlorides and albumin was determined throughout the course of the nephrosis. The alterations in the excretion of the urinary substances were correlated with the changes in the concentration of some of these substances in the blood and with the anatomic alterations in the kidneys.

REVIEW OF THE LITERATURE

Most of the previous work on experimental uranium nephrosis has been reviewed in the excellent monograph of MacNider;[1] therefore, only the literature directly pertinent to the present report will be discussed. The occurrence of glycosuria and polyuria in the acute nephrosis following the administration of uranium nitrate was first observed by Chittenden, Hutchinson and Lambert.[2] Some workers (Meyner[3] and Fleckseder[4]) said they considered the glycosuria to be secondary to an accompanying hyperglycemia, but it was shown by others (Lépine and

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1. MacNider, W. de B.: Physiol. Rev. **4**:595, 1924.

2. Chittenden, R. H., and Hutchinson, M. T.: Tr. Connecticut Acad. Arts & Sc. **7**:261, 1887. Chittenden, R. H., and Lambert, A.: Ztschr. f. Biol. **25**:513, 1889.

3. Meyner, H.: Der Kohlehydratverbrauch bei Uranvergiftungen, Inaug. Dissert., Würzburg, P. Scheiner, 1898.

4. Fleckseder, R.: Arch. f. exper. Path. u. Pharmakol. **6**:54, 1907.

Boulud,[5] Blanck,[6] Frank,[7] Pollak [8] and Wallace and Myers [9]) that the kidney in uranium poisoning could excrete sugar when the level of sugar in the blood was normal or even subnormal. Pohl [10] observed in his animals that, in addition to the glycosuria and polyuria reported by Chittenden, there was an increased excretion of chlorides. Wallace and Myers, on the other hand, could find no relationship between the excretion of sugar and that of chlorides. The kidneys of Pohl's animals showed severe tubular destruction, but the glomeruli were intact. Austin and Eisenbrey [11] observed diuresis associated with an increased elimination of chlorides when small doses of uranium nitrate were given. Later in the course of the poisoning the excretion of chlorides was reduced. Weber [12] noted an increase in the volume of urine and a response to diuretics that were greater than in his normal controls. From the work of Christian, Smith and Walker,[13] Christian and O'Hare,[14] Pearce,[15] MacNider [16] and Aschoff and Suzuki [17] it is known that the injury induced by uranium is largely tubular and that the principal site of damage is the epithelium of the third and distal portion of the tubule. The glomeruli are much less susceptible to injury, and it is only after several days of uranium poisoning that glomerular changes can be demonstrated histologically.

METHODS AND MATERIAL

Twelve female dogs weighing from 6.25 to 17.75 Kg. were used. The animals fasted for a preliminary period of at least one day and for the entire course of the experiment but were allowed drinking water as desired.

After a control period of from four hours to three days, each animal was given a single subcutaneous injection of uranium nitrate (15 mg. per kilogram of body weight, except in one instance in which 10 mg. per kilogram of body weight was given). Throughout the experimental and control periods frequent

5. Lépine, R., and Boulud: Rev. de méd., Paris **24**:1, 1904.
6. Blanck, S.: Med. Klin. **1**:1144, 1905.
7. Frank, E.: Arch. f. exper. Path. u. Pharmakol. **72**:387, 1913.
8. Pollak, L.: Arch. f. exper. Path. u. Pharmakol. **64**:415, 1911.
9. Wallace, G. B., and Myers, H. B.: J. Pharmacol. & Exper. Therap. **5**:511, 1914.
10. Pohl, J.: Arch. f. exper. Path. u. Pharmakol. **67**:233, 1912.
11. Austin, J., and Eisenbrey, A. B.: J. Exper. Med. **14**:366, 1911.
12. Weber, S.: Arch. f. exper. Path. u. Pharmakol. **54**:1, 1906.
13. Christian, H. A.; Smith, R. M., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:468 (Oct.) 1911.
14. Christian, H. A., and O'Hare, J. P.: J. M. Research **28**:227, 1913.
15. Pearce, R. M.: The Problems of Experimental Nephritis, Arch. Int. Med. **5**:133 (Feb.) 1910.
16. MacNider, W. de B.: Am. J. M. Sc. **178**:449, 1929.
17. Aschoff, L., and Suzuki: Verhandl. d. deutsch. path. Gesellsch. **15**:199, 1912.

determinations were made of the sugar, urea or nonprotein nitrogen content of the blood and the sugar and total nitrogen contents of the urine. Likewise, in two experiments the urinary output of albumin and chlorides was quantitatively determined.

The animals were kept in metabolism cages which permitted accurate collections of all urinary specimens. At the end of each experimental period the animals were catheterized. The bladder was rinsed thoroughly with a measured amount of sterile water, and the volume of urine was estimated. The amount of drinking water ingested during each period was determined.

Seven of the animals were permitted to live until anuria developed and death occurred, four animals were killed with rapid chloroform anesthesia when the glycosuria was estimated to be at its greatest height and one dog was killed at the onset of the anuric stage. Immediately after the death of the animals the kidneys were removed and placed in a dilute solution of formaldehyde U. S. P. (1:10).

The total nitrogen content of the urine was determined by the usual macromethod of Kjeldahl, the nonprotein nitrogen content of the blood by the micromethod of Kjeldahl, the urea content of the blood by the method of Folin and Denis, the sugar content of the urine by the procedures of Benedict and of Shaffer and Hartmann and the sugar content of the blood by the method of Shaffer and Hartmann. The Volhard-Arnold method was used for the determination of the urinary chlorides. The quantitative estimation of the urinary albumin was accomplished by determining the reduction in the amount of total nitrogen in the urine when the albumin was removed. The albumin was removed by boiling the urine after acidification with acetic acid. The filtrates of all specimens of urine treated in this manner showed no albumin.

The renal tissue was fixed in solution of formaldehyde, sectioned by the paraffin technic and stained with hematoxylin and eosin

For the sake of economy of space, detailed protocols are not presented. Instead, charts showing data observed in typical experiments are given. These data are representative of all the observations, as the findings in the comparable experiments were essentially the same.

OBSERVATIONS

Stage of Glycosuria.—In all experiments sugar first appeared in the urine at about the sixth hour after the administration of the uranium nitrate. By the tenth hour the glycosuria had become well established, and at about the twenty-fourth hour the excretion had reached its maximum of from 0.128 to 0.314 Gm. of sugar per hour. Thereafter, it decreased steadily, and at about the thirty-sixth to the seventy-second hour the glycosuria disappeared. Accompanying the glycosuria was an increase in the volume of urine. As the glycosuria decreased the volume of urine became smaller, and in most instances anuria developed rapidly. However, in one experiment moderate amounts of urine continued to be excreted for twenty-seven hours after the glycosuria had disappeared.

In no experiment did the concentration of blood sugar during the period of glycosuria rise above the normal control values. On the other hand, there was a slight decrease in the level of the blood sugar

in most instances while sugar was being excreted by the kidneys. Figure 1 shows this relationship and is representative of the findings in all the experiments. In the two animals for which the excretion of chlorides was determined, the urinary chloride content was observed to increase at about the same time that glycosuria was established. Thus for dog

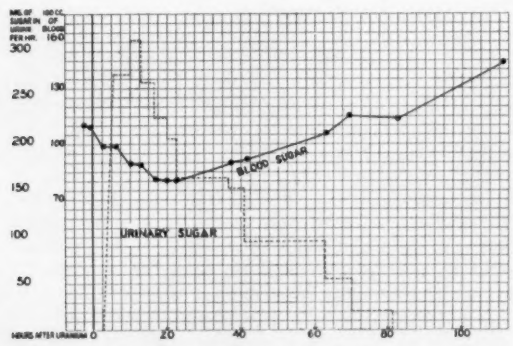

Fig. 1 (dog 189).—The effect of uranium nitrate on the level of the blood sugar and on the urinary excretion of sugar.

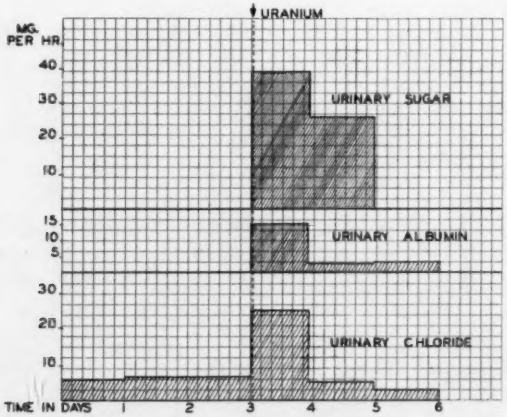

Fig. 2 (dog 225).—The excretion of urinary chlorides, sugar and albumin after the administration of uranium nitrate.

224 the urinary chloride content increased from 0.006 Gm. per hour (calculated as sodium chloride) to 0.019 Gm. per hour during the period of twenty-three hours in which from 0.06 to 0.043 Gm. of sugar was being eliminated hourly by the kidneys. However, the glycosuria of both dogs persisted for about twenty-four hours after the excretion

of chloride had returned to its former level or had decreased to a level lower than that of the control period. Figure 2 illustrates the data for dog 225, which are essentially similar to those observed for dog 224.

The urine contained albumin as early as the third hour following the administration of uranium nitrate. The albuminuria preceded the establishment of the glycosuria and persisted until the animals became anuric. The excretion of albumin appeared to bear no relation to the glycosuria. Thus, in the experiment on dog 225, 0.015 Gm. of albumin nitrogen was excreted per hour, while 0.039 Gm. of sugar was being eliminated per hour by the kidneys. However, in the following period, when 0.026 Gm. of sugar was still being excreted each hour, the output of albumin nitrogen had fallen to 0.002 Gm. per hour (fig. 2).

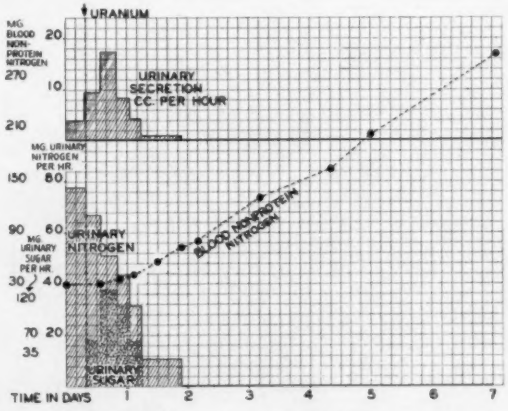

Fig. 3 (dog 197).—The effect of uranium nitrate on the volume of urine, on the excretion of total urinary nitrogen and sugar and on the level of nonprotein nitrogen in the blood. The relationships between the changes in the volume of urine and those in the content of urinary sugar and between the changes in the urinary nitrogen and those in the nonprotein nitrogen of the blood are shown.

The development of albuminuria preceded any increase in the concentration of urea or nonprotein nitrogen in the blood. For example, in dog 197 the blood urea was of normal value twenty-four hours after the injection of uranium nitrate, although both albuminuria and glycosuria had been well established for over six hours. After this period the concentration of nonprotein nitrogen in the blood increased gradually until glycosuria had disappeared and anuria had developed. After the establishment of anuria the rise in the nonprotein nitrogen level of the blood was rapid (fig. 3).

The kidneys of all four dogs killed when the glycosuria was estimated to be at its height showed similar histologic changes. The main site of

damage was the convoluted tubules. There was beginning degeneration, with cloudy swelling of the epithelium of the convoluted tubules, but no actual necrosis. There was moderate congestion throughout the

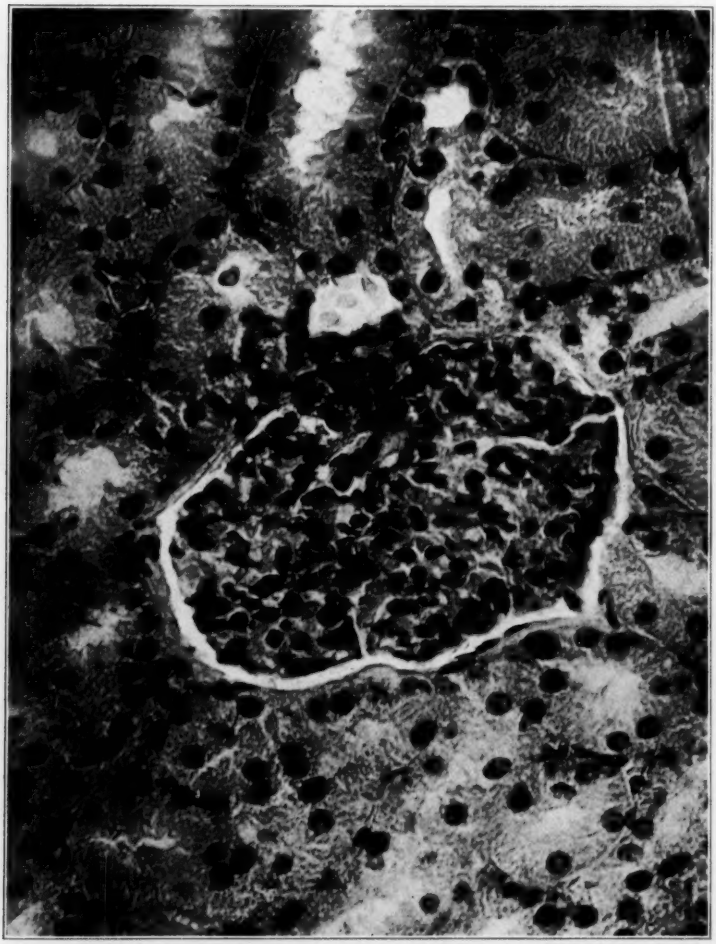

Fig. 4 (dog 194).—Stage of glycosuria. Section of the kidney twenty-four hours after the administration of uranium nitrate. The urinary excretion of sugar was 0.272 Gm. per hour, and the sugar content of the blood was 98 mg. per hundred cubic centimeters.

kidney, including the glomeruli, but the glomeruli otherwise appeared to be normal (fig. 4).

State of Anuria.—In all eight animals which were permitted to live after the glycosuria had disappeared anuria developed in the course of a few days. Although the urinary output diminished as the glycosuria

Fig. 5 (dog 191).—Stage of anuria. Section of the kidney nine days after the administration of uranium nitrate.

decreased, the volume of urine did not fall below the level of the control period until the glycosuria had disappeared. Thereafter, the development of anuria proceeded rapidly.

After the establishment of anuria the concentration of nonprotein nitrogen in the blood increased rapidly until shortly before the death of the animal, when there was as much as 299 mg. of nonprotein nitrogen in each hundred cubic centimeters of blood. The concentration of

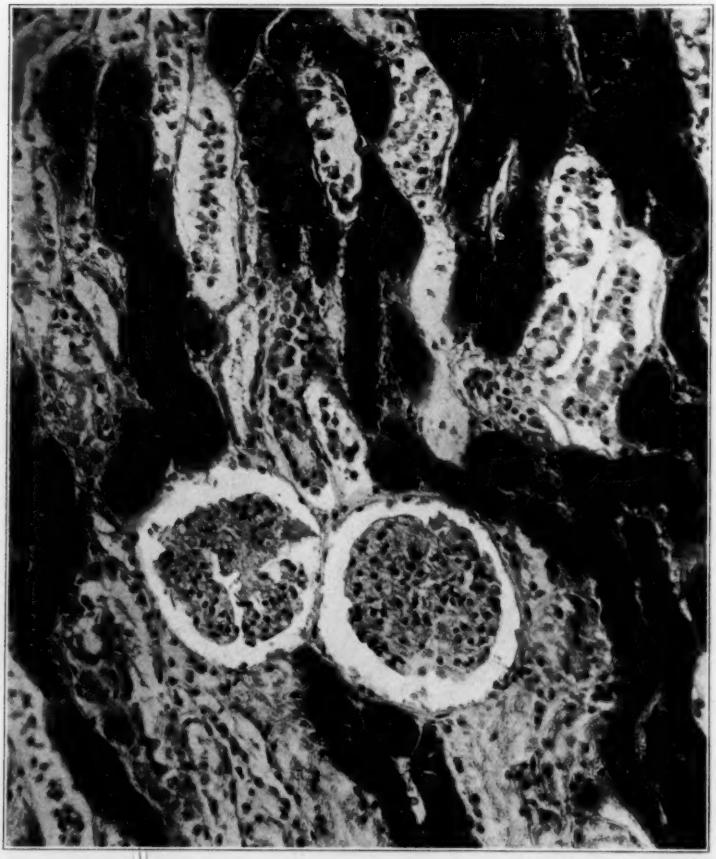

Fig. 6 (dog 192).—Stage of anuria. Section of the kidney eight days after the administration of uranium nitrate, showing calcium deposition (black). The dog was anuric for six days. There was 150 mg. of sugar per hundred cubic centimeters of blood.

sugar in the blood likewise rose, although the increase was much less rapid. It increased steadily and reached an average value of 128 mg. per hundred cubic centimeters. The kidneys of all the animals dying

in the anuric stage showed essentially the same anatomic changes. In dog 192, which lived for six days after total anuria had been established, the pathologic alterations were more advanced than in the other seven animals in this group. The main site of injury was the convoluted tubule. Necrosis and desquamation of the epithelium were noted, with fusing of the cells and obliteration of their margins. Many of the cells were without nuclei. In some places granular débris filled the lumens of the tubules, and vacuoles of varying sizes were noticeable in the epithelial débris. In dog 192 there was considerable calcium formation in the convoluted tubules, the picture resembling that seen in mercury bichloride poisoning. In the other animals in this group early deposition of calcium was seen in the tubules. The straight tubules, on the whole, were uninvolved, except for occasional early fatty degeneration of the epithelium. The glomeruli in these animals were only moderately involved. There was moderate congestion with hemorrhages, and in some places the tufts were shrunken and had pulled away from Bowman's capsule. Occasional hyaline droplets were seen in the lumen of the capsule. On the whole, the glomeruli were well preserved.

COMMENT

The experiments indicate that the glycosuria occurring early in the course of acute nephrosis induced by uranium is of renal origin and is related to early injury to the tubular epithelium. Moreover, the increase in the excretion of water and chlorides could be ascribed to the same changes. Wearn and Richards [18] have shown that in the frog water, sugar and chlorides are reabsorbed from the glomerular filtrate by the tubules. An impaired ability of the tubular epithelium to reabsorb these constituents in uranium poisoning would explain the results observed in these experiments. Such an explanation would be compatible with the changes demonstrated by histologic examination. The functional alterations in this stage of the nephrosis appear to be similar to those observed in phlorhizin poisoning (Deuel, Wilson and Milhorat [19] and Richards [20]) and in nephrosis occurring in patients (Hawkins, MacKay and Van Slyke [21]). The latter investigators found the kidneys to be abnormally permeable to dextrose in the "tubular" type of nephritis (nephrosis with considerable albuminuria), whereas in the glomerulo-

18. Wearn, J. T., and Richards, A. N.: Am. J. Physiol. **71**:209, 1924.

19. Deuel, H. J.; Wilson, H. E. C., and Milhorat, A. T.: J. Biol. Chem. **74**:265, 1927.

20. Richards, A. N., in Harvey Lectures, 1934-1935, Baltimore, Williams & Wilkins Company, 1936, p. 93.

21. Hawkins, J. A.; MacKay, E. M., and Van Slyke, D. D.: J. Biol. Chem. **78**:xxiii, 1928.

nephritic type no glycosuria developed after the administration of dextrose unless there was a considerable increase in the sugar content of the blood.

The urinary changes occurring late in the course of the poisoning (the retention of the various urinary substances and finally the complete anuria) can find a partial explanation in the idea advanced by MacNider,[22] who stated that he thought the anuria was the result of occlusion of the lumen of the tubules by débris. On the other hand, the mechanism in uranium poisoning is probably similar to that observed by Richards [23] following the administration of mercury bichloride in frogs. In frogs poisoned with mercury, Richards demonstrated a normal glomerular function, but the resorption of the glomerular filtrate proceeded at such a rapid rate that anuria resulted. However, the early retention of nitrogen might conceivably be due to the glomerular changes, as was suggested by Milhorat and Deuel.[24]

SUMMARY

The urinary changes and the anatomic alterations in the kidneys were studied during the various stages of the acute nephrosis induced by uranium nitrate. Dogs given large doses of uranium showed evidence of extensive renal involvement within a few hours after injection of the salt.

Glycosuria appeared early and was accompanied with an increase in the urinary elimination of water and chlorides. In the main, these changes occurred concomitantly. During the periods when the glycosuria was at its height, larger amounts of water and chlorides were eliminated, whereas the urine contained smaller amounts of water and chloride during the period in which the glycosuria decreased and finally disappeared. The level of the blood sugar during this stage remained normal or fell to slightly subnormal values. The histologic alterations in the kidneys were confined to early degenerative changes in the tubular epithelium and suggest that the changes in the urinary elimination of sugar, water and chlorides are due to an impaired ability of the tubules to resorb these substances from the glomerular filtrate.

Albuminuria occurred early, but unlike the glycosuria, which disappeared after a few days, it persisted as long as urine was being excreted. The output of nitrogen was progressively decreased. This impairment was followed by an increase in the concentration of nonprotein nitrogen in the blood.

22. MacNider, W. de B.: J. Pharmacol. & Exper. Therap. **3**:423, 1912.

23. Richards, A. N.: Methods and Results of Direct Investigations of the Function of the Kidney, Baltimore, Williams & Wilkins Company, 1929.

24. Milhorat, A. T., and Deuel, H. J., Jr.: Proc. Soc. Exper. Biol. & Med. **25**:294, 1928.

Anuria developed soon after the glycosuria had disappeared. Shortly after the establishment of anuria the amount of nonprotein nitrogen in the blood increased rapidly, and the sugar content of the blood rose to above its previous level. The kidneys at this stage showed advanced degeneration of the tubular epithelium and only moderate changes in the glomeruli. It is suggested that the anuria might be due to the complete resorption of the glomerular filtrate by the damaged tubules.

Dr. Elise L'Esperance, of the Department of Pathology, assisted in preparing and interpreting the microscopic slides.

CARCINOMA OF THE ISLANDS OF LANGERHANS WITH HYPOGLYCEMIA AND HYPERINSULINISM

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The syndrome commonly known as spontaneous hypoglycemia was recognized by Seale Harris [1] in 1924 and was attributed by him to "hyperinsulinism," in contrast to the supposed "hypo-insulinism" of diabetes. The possibility of true hyperinsulinism was first demonstrated in 1927 by Wilder, Allan, Power and Robertson [2] in a report of a case of severe hypoglycemia in which carcinoma of the islands of Langerhans with extensive metastasis to the liver and lymph nodes was noted at necropsy. The cells of the metastatic nodules in the liver bore a striking resemblance to the cells of the islands of Langerhans, and an extract of the hepatic nodules was found to possess the property of markedly lowering the concentration of sugar in the blood when injected into rabbits.

Since that report there have appeared in the literature (recently reviewed by Whipple and Frantz [3] and by Wilder [4]) numerous descriptions of cases of spontaneous hypoglycemia. In several instances the condition has been attributed to hyperfunctioning adenomas of the islands of Langerhans, since surgical removal of one or more tumors from the pancreas resulted in complete recovery and cessation of symptoms. The first case of this kind was that of Howland, Campbell,

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1. Harris, Seale: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729-733 (Sept. 6) 1924.

2. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348-355 (July 30) 1927.

3. Whipple, A. O., and Frantz, Virginia K.: Adenoma of Islet Cells with Hyperinsulinism: A Review, Ann. Surg. **101**:1299-1335 (June) 1935.

4. Wilder, R. M.: Spontaneous Hypoglycemia, Internat. Clin. **3**:143-163 (Sept.) 1936.

Maltby and Robinson [5] (1929). The tumor was extracted for insulin, and the extract was tested on mice by Professor C. H. Best. Of eight mice which were given injections, five had insulin convulsions, and two of the animals died. The extract thus undoubtedly contained insulin, but accurate assay was not attempted, because of lack of material as well as lack of any accurate knowledge of the amount of insulin extractable from the normal pancreas of man. In the other cases in which removal of an island cell tumor from the pancreas has resulted in cure of the hypoglycemic condition, the tissue removed has been extracted in three instances (Graham and Womack,[6] 1933; Derick, Newton, Schulz, Bowie and Pokorny,[7] 1933, and Liu, Loucks, Chou and Chen,[8] 1936), and more or less conclusive evidence has been obtained of the presence of insulin activity in the extracts.

Tumors removed at operation in some of these cases were considered to be carcinomas with a low grade of malignancy (Howland and others [5] and Graham and Womack [6]), but only four cases of carcinoma of the islands of Langerhans with metastasis to the liver have been described. The first of these, subsequent to the case of Wilder, Allan, Power and Robertson,[2] was reported by Hamdi,[9] who discovered the carcinoma at necropsy. The metastatic nodules in the liver resembled morphologically the islands of Langerhans in the pancreas. However, there was no clinical history of the syndrome of hypoglycemia, and the metastatic growths were not examined for insulin. In the second case, that of Judd, Faust and Dixon,[10] there was a definite history of the hypoglycemic syndrome, and a specimen taken for biopsy from a carcinomatous nodule in the liver was histologically characteristic of an island cell tumor. Examination of the tissue for insulin was not attempted. The third case, reported

5. Howland, Goldwin; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet Cell Tumor of the Pancreas, with Operation and Cure, J. A. M. A. **93**:674-679 (Aug. 31) 1929.

6. Graham, E. A., and Womack, N. A.: The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and to Other Conditions, Surg., Gynec. & Obst. **56**:728-742 (April) 1933.

7. Derick, C. L.; Newton, F. C.; Schulz, R. Z.; Bowie, M. A., and Pokorny, N. A.: Spontaneous Hyperinsulinism: Report of a Case of Hyperinsulinism Cured by Surgical Intervention, New England J. Med. **208**:293-298 (Feb. 9) 1933.

8. Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism: Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, J. Clin. Investigation **15**:249-260 (May) 1936.

9. Hamdi, H.: Ein insulargenetisches Pankreascarcinom (Insulom), Ztschr. f. Krebsforsch. **37**:411-413, 1932.

10. Judd, E. S.; Faust, L. S., and Dixon, R. K.: Carcinoma of the Islands of Langerhans with Metastasis to the Liver Producing Hyperinsulinism: Report of Case, West. J. Surg. **42**:555-557 (Oct.) 1934.

by Bickel, Mozer and Junet,[11] was an interesting one, that of a man who had had severe diabetes for more than a year and who suddenly showed a tendency toward persistent and marked hypoglycemia associated with attacks of unconsciousness. At necropsy a carcinoma of the pancreas was present, with multiple metastatic growths in the liver. The cellular structure of the growths was similar to that of the islands of Langerhans. An extract of the tumor of the pancreas when tested on dogs was found to contain "insuline en quantité notable," but concerning extracts of the metastatic growths in the liver the report was "absence d'insuline." No details concerning the procedure for extraction and testing were given.

To these cases we are now able to add a fifth one, of carcinoma of the islands of the pancreas with metastasis to the liver. This case is one of spontaneous hypoglycemia, attributable probably to true hyperinsulinism, since tests of extracts of the metastatic nodules in the liver gave unequivocal evidence of insulin-like activity. The studies we have made confirm the observations reported in the case of Wilder and his associates and constitute, we believe, the second demonstration of the presence of insulin in malignant tissue originating from the islands of Langerhans but not situated directly in the pancreas itself.

REPORT OF A CASE

A married woman, 41 years of age, came to the Mayo Clinic on Jan. 30, 1935, having been referred by Dr. L. E. Cooley, of Dubuque, Iowa, who had made the diagnosis. She had been in excellent health until three months previously, at which time she had noticed that on arising in the morning she felt light headed, dizzy and slightly confused mentally. Often there was associated profuse perspiration, and the entire syndrome lasted from two to three hours, after which it gradually disappeared. Soon after the onset of this condition, the patient discovered that a glass of milk taken in the course of the attack would give partial relief. However, at that time she did not realize that her habit of not eating breakfast was associated with these attacks.

On December 1, a month after the onset of her symptoms, she was busy preparing for a large dinner party and did not take time to eat in the course of the day. A few minutes after she took her seat at the table that evening she was overcome by a feeling of extreme weakness. This sensation was almost immediately accompanied with marked mental confusion and by profuse perspiration. Fifteen minutes later she became completely unconscious, with associated generalized muscular rigidity, which was more marked in the right arm and leg. She remained in this state for four hours and then without treatment gradually recovered. The only residual manifestation was moderate weakness of the right arm and leg. The

11. Bickel, Georges; Mozer, J. J., and Junet, R.: Diabète avec dénutrition grave: Disparition de la glycosurie et atténuation progressive de l'hyperglycémie à la suite du développement d'un carcinoma insulaire du pancréas avec métastases hépatiques massives, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:12-21 (Jan. 11) 1935.

following day she did not feel well and therefore remained in bed and ate nothing. That evening she again lost consciousness in a manner similar to that of the previous night, and she remained in a comatose state for thirty hours. At the end of this period her condition became alarming, and as supportive treatment she was given solution of dextrose intravenously. The injection restored her to full consciousness almost immediately. However, weakness of the right side remained, as did slight thickness of speech, several hours longer. Her illness was then recognized as a state of spontaneous hypoglycemia, and she was consequently given frequent feedings of a diet high in carbohydrate. On this regimen she experienced no more attacks, except for a mild attack one morning, which was attributable to delay in eating breakfast. The level of blood sugar at that time was found to be 30 mg. per hundred cubic centimeters. The patient said that by trial and error she had determined that the maximal time over which she could remain free from symptoms between feedings was from ten to twelve hours.

The past history was not remarkable except for hysterectomy and oophorectomy on the left side performed in 1933 for leiomyomas of the uterus. Physical examination disclosed nothing abnormal except increased deep reflexes. The edge of the liver was not palpable, and no abdominal masses were felt. The blood pressure

TABLE 1.—*Data Showing the Effect of Dextrose*

Time	Blood Sugar, Mg. per 100 Cc.
8:00 a. m.	40
57 Gm. of dextrose (orally)	
8:30 a. m.	132
9:00 a. m.	112
10:00 a. m.	146
11:00 a. m.	59

was 142 mm. of mercury systolic and 94 diastolic. The urine was analyzed many times and was found to contain albumin varying between grade 1 and grade 2, with an occasional pus cell. The erythrocyte count was 4,380,000 and the leukocyte count 7,500 cells per cubic millimeter of blood. The differential count was 75 per cent neutrophils, 19.5 per cent lymphocytes, 5 per cent monocytes and 0.5 per cent eosinophils. A Wassermann test of the blood gave a negative reaction. The blood showed 14 mg. of urea and 2.43 mg. of uric acid per hundred cubic centimeters. A roentgenogram of the skull appeared normal. The results of a dextrose tolerance test were definitely significant. The level of blood sugar during fasting was 40 mg. per hundred cubic centimeters. Two hours after the oral administration of 57 Gm. of dextrose it rose to 146 mg., but one hour later it had again receded to 59 mg. per hundred cubic centimeters (table 1). If food was withheld for longer than ten hours, symptoms of hypoglycemic shock developed. At the end of that interval the patient would become nervous and confused, and if carbohydrate were not administered immediately she would quickly pass into a semicomatose state. This observation verified the patient's own statement.

In order to determine the presence and availability of the store of glycogen in the liver, epinephrine and solution of posterior pituitary (double U. S. P. strength) were injected subcutaneously in two different studies (tables 2 and 3). The definite rise in the level of blood sugar after the injection of epinephrine was felt to be evidence that glycogen was being discharged into the blood stream from the liver. However, the solution of pituitary had no effect, and the blood sugar level

continued to fall, so that at the end of two hours it became necessary to administer orange juice and milk in order to avoid a hypoglycemic reaction. The function of the liver was found to be unimpaired, as disclosed by the bromsulphalein tolerance, the galactose tolerance and the hippuric acid test. The van den Bergh reaction was direct, and the value for serum bilirubin was 1 mg. per hundred cubic centimeters.

Because the patient was suffering definite attacks of spontaneous hypoglycemia and because there was no evidence of impairment in the ability of the liver to store and discharge glycogen, it was felt that a state of hyperinsulinism existed, due probably to excess secretion caused by a neoplasm of the islands of Langerhans. Therefore, on February 6, after intravenous administration of 100 Gm. of dextrose, Dr. Judd performed an abdominal exploratory operation. The liver was found to contain numerous carcinomatous metastatic growths. The pancreas was so sur-

TABLE 2.—*Data Showing the Effect of Epinephrine*

Time	Blood Sugar, Mg. per 100 Cc.
3:00 p. m.	85
1 cc. of solution of epinephrine hydrochloride (1:1,000), subcutaneously	
4:00 p. m.	117
5.00 p. m.	89

TABLE 3.—*Data Showing the Effect of Solution of Pituitary*

Time	Blood Sugar, Mg. per 100 Cc.
3:00 p. m.	73
1 cc. of solution of pituitary (intramuscularly)	
3:30 p. m.	58
4:00 p. m.	50
5:00 p. m.	100*

* Orange juice and milk given ten minutes before specimen of blood was taken.

rounded by dense masses of enlarged lymph nodes that it was impossible to determine definitely whether or not that organ was the site of the primary carcinoma. Microscopic examination of a specimen removed from the liver verified the diagnosis of carcinoma, probably primary in the islands of Langerhans. The operation was performed with the patient under spinal anesthesia; the entire procedure lasted twenty-five minutes and was completed at 10: 15 a. m. At 10: 50 a. m. the concentration of blood sugar was 133 mg. per hundred cubic centimeters, and at 1 p. m. 102 mg., and by 3 p. m. it had fallen to 92 mg. Dextrose solution was then administered intravenously every ten hours, and after forty-eight hours the patient was again given the preoperative diet. An uneventful recovery ensued, and she was dismissed from the clinic on February 25. She died in Salt Lake City on July 10.

Gross Postmortem Observations.—Necropsy was performed by one of us (M. C. L.) at Salt Lake City approximately one hour after death had occurred. The heart was normal. The lungs revealed a slight amount of passive congestion. The liver contained innumerable firm, reddish gray nodules varying from 0.5 to 4 cm. in diameter, so that the entire organ was enlarged to approximately one and

a half times its normal size. The pancreas was surrounded by a mass of enlarged lymph nodes which were of firm consistency and reddish on the cut surface. The pancreas itself contained no nodules but was unusually firm. Both the pancreatic and the common bile duct were patent. The lymph nodes in the region of the mesentery and along the course of the abdominal aorta also were enlarged and of the same texture and color as those surrounding the pancreas. The gastric mucosa contained multiple large ecchymotic areas in its mucosal surface. The uterus, both fallopian tubes and the left ovary were absent. The right ovary contained a hemorrhagic cyst, approximately 3 cm. in diameter. The other abdominal viscera were not remarkable. Immediately after completion of the examination, the entire right lobe of the liver, half the pancreas and a mass of the enlarged lymph nodes were packed in solid carbon dioxide and shipped to Rochester, Minn., by airplane. On arrival they were solidly frozen and in a state of perfect preservation. The liver was immediately sectioned, and portions to be extracted were excised. Sections for microscopic study were taken from numerous areas in the tail of the pancreas, lymph nodes and liver and were fixed in Orth's solution. They were then blocked in paraffin and stained with hematoxylin and eosin. Portions of the liver were fixed in alcohol and stained for glycogen with Best's carmine dye.

Microscopic Postmortem Observations.—The normal pancreatic tissue was extensively replaced by masses of tumor cells which were arranged almost entirely in islands and thin strands (fig. 1 *A*). The islands varied in size from that of a normal pancreatic island to that of an island at least twenty times larger. They were roughly circular in outline, and their cells were closely packed. In other areas fibrous connective tissue trabeculae separated the tumor cells into short thin strands. Nowhere was there any evidence of an attempt to form ducts or acini. Each group of tumor cells was surrounded by a clear space, lined with endothelial cells and frequently containing erythrocytes. However, there was no pronounced increase in the vascularization of the neoplastic tissue. The cellular characteristics were those of a moderately slow-growing carcinoma, with cells of uniform size and only a sparse scattering of large cells and mitotic figures. No multinucleated giant cells were seen, and the nuclei were not remarkably hyperchromatic. The absence of necrosis in the centers of the masses of tumor cells was evidence that cellular proliferation was not destroying the blood supply. Normal pancreatic acini were seen in only small areas and were surrounded by heavy masses of fibrous tissue, which appeared to be slowly choking them. In these areas there were also a few normal islands of Langerhans. One of the most striking features of the microscopic study was the difficulty experienced in differentiating the tumor islands from the normal islands.

All the lymph nodes which were sectioned were composed almost entirely of carcinoma, a few thin strands of lymphocytes around the periphery being the only certain means of identifying them. The distribution and cellular structure of the carcinoma in the nodes were practically identical with those of the growth in the pancreas.

The tumorous growths in the liver (fig. 1 *B*) revealed a most unusual histologic picture. In addition to the large, grossly visible metastatic growths there were innumerable cancerous nodules of microscopic size. They were circular to oval, with the cells packed in solid masses and with no tendency to form acini, thus giving the tumor nodules the appearance of large pancreatic islands. Each of the islands was sharply delineated by an encircling clear space, which could not be definitely identified as a blood vessel because of the absence of erythrocytes within its lumen. The larger island-like metastatic growths had undergone central

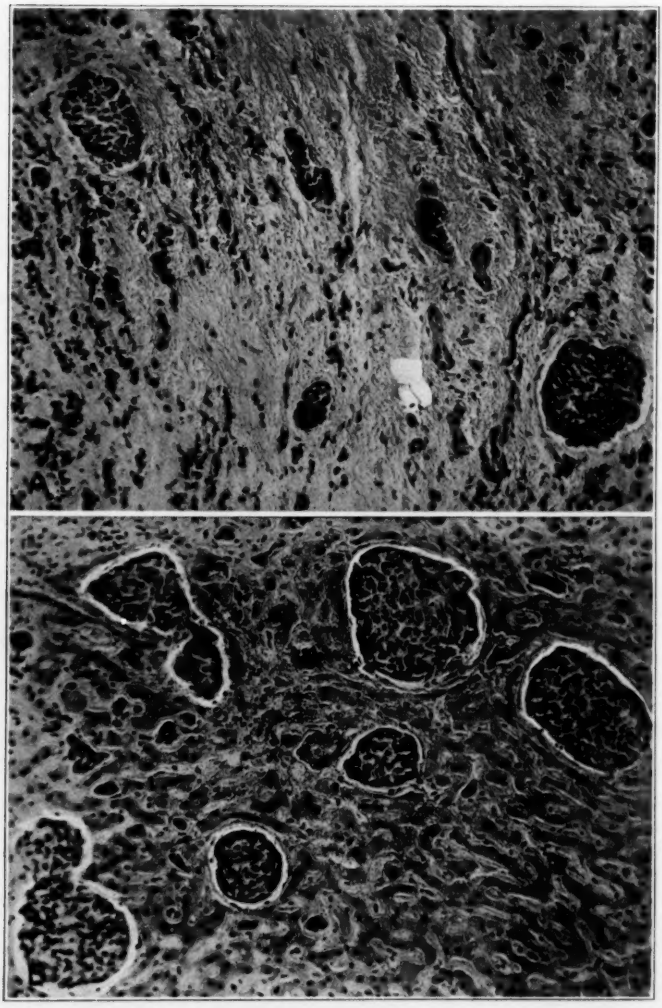

Fig. 1.—*A*, island cell carcinoma in the pancreas; *B*, metastasis in the liver from an island cell carcinoma in the pancreas; × 125.

necrosis, and only a band of intact cells remained around the periphery. The cells in the more extensive areas of tumor had been compressed into elongated strands by heavy sheets of hyalinized fibrous tissue, and in these areas many capillaries were visible. The carcinoma in the liver appeared to be more malignant than in either the pancreas or the lymph nodes. The cells were more irregular in size and shape, and there were numerous giant cells, some of which were multinucleated. Mitotic figures were more plentiful, and all the nuclei were deeply basophilic.

From the morphologic standpoint it appeared that the tumor had originated as a slow-growing neoplasm in the pancreas, and later, as the speed of growth had increased, it had spread to the surrounding lymph nodes and finally to the liver, where it exhibited itself in the full bloom of a rapidly growing carcinoma. Robertson examined the microscopic sections and was of the opinion that this tumor had grown more slowly than the one which occurred in the case described in 1927 [2] and that its morphologic appearance was even more characteristic of tumor of the islands of Langerhans than was that of the other tumor.

At the time the liver was originally sectioned four specimens had been taken from widely separated areas; these had been fixed in absolute alcohol and then stained with Best's carmine dye. They were bright pink, thus proving the presence of large deposits of glycogen. No quantitative analysis for glycogen was carried out.

Extraction of Metastatic Nodules of the Liver for Insulin.—The method of extraction used was that of Best, Jephcott and Scott,[12] a procedure which they described as yielding the "maximal amounts of insulin from the pancreas." The cancerous tissue was carefully separated from the frozen liver, 127 Gm. being finely ground and placed immediately in acid alcohol. At the same time 112 Gm. of adjacent normal-appearing hepatic tissue was freed of cancer nodules as completely as possible and treated similarly. Each extract when completed was made up to a volume of 200 cc. For testing, four rabbits (1 to 4) weighing 2, 2.5, 2.6 and 2.3 Kg., respectively, were selected and made to fast for twenty-four hours. Rabbits 1 and 2 were given subcutaneous injections of 10 cc. of the extract of the normal tissue of the liver (liver extract), and rabbits 3 and 4 were given 5 cc. of the extract of cancerous tissue of the liver (tumor extract). The level of the blood sugar before and at intervals after injection was determined by the method of Folin and Malmros [13] from 0.1 cc. samples of blood drawn from the marginal vein of the ear. After six days the experiment was repeated, this time rabbits 1 and 2 being given 15 cc. of the tumor extract and rabbits 3 and 4 15 cc. of the liver extract.

The levels of blood sugar before and after injection in these two series of experiments are shown in figures 2 and 3. It is to be noted, first, that the values for blood sugar during fasting were all within normal limits, the highest being less than 130 mg. per hundred cubic centimeters, and, second, that remarkably small changes in the concentration of blood sugar occurred after the injections of liver extract. This was to be expected, since it has been established by the work of

12. Best, C. H.; Jephcott, C. M., and Scott, D. A.: Insulin in Tissues Other Than the Pancreas, Am. J. Physiol. **100**:285-294 (April) 1932.

13. Folin, Otto, and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115-120 (July) 1929.

Best, Jephcott and Scott that normal hepatic tissue, as well as animal and vegetable tissues in general, does not contain insulin that can be extracted by the methods now available. Consequently, the curves obtained after the injection of the inactive liver extracts serve as excellent controls and illustrate the small fluctuations in blood sugar level under the conditions of our experiments. In contrast to these control

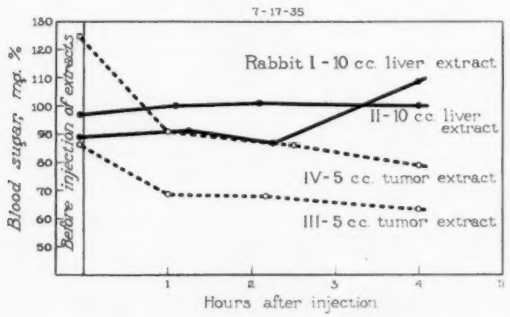
7-17-35
Blood sugar, mg. %
Before injection of extracts
Rabbit I - 10 cc. liver extract
II - 10 cc. liver extract
IV - 5 cc. tumor extract
III - 5 cc. tumor extract
Hours after injection

Fig. 2.—First assay of the extracts.

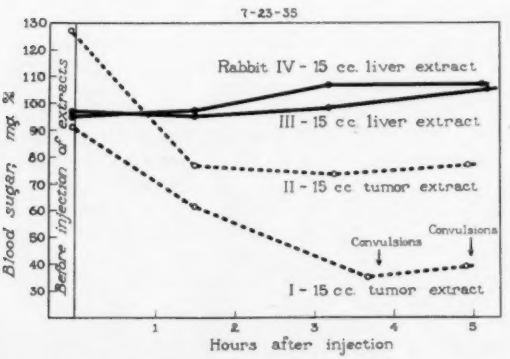

Fig. 3.—Second assay of the extracts.

values, the value for blood sugar was lowered significantly for each of the four rabbits after the injection of the tumor extract, and in rabbit 1 typical convulsions ensued. This animal recovered completely when a solution containing 2 Gm. of dextrose was injected subcutaneously after a second series of convulsions. The evidence, therefore, for the presence of an insulin-like substance in the extract of the tumor nodules of the liver may be taken as conclusive.

The recovery of a blood sugar-lowering substance from the metastatic tumors of the liver thus confirms the microscopic evidence for the presence of islands of Langerhans in the tumors and demonstrates the capacity of these islands to function. Conversely, the failure of Best, Jephcott and Scott to obtain extracts capable of lowering the blood sugar level from any tissue except the pancreas justifies the view that the active substance in our extract of tumor tissue was actually insulin. Although the data are not extensive enough to warrant quantitative calculation of the amount of insulin present, the estimate of about 2.5 units for each 15 cc. of extract seems conservative. On this basis the metastatic tumor tissue yielded, under the conditions of these experiments, around 260 clinical units of insulin per kilogram.

COMMENT

The hypoglycemic condition in this case seems clearly established as attributable to true "hyperinsulinism." The liver was extensively invaded by cancerous growth, yet at least a third of the organ was normal hepatic tissue; the function of this tissue was normal, as judged by the various tests of liver function. Moreover, ample stores of glycogen were present, as indicated by microscopic examination of the tissue, and could be mobilized, as indicated by the increase in blood sugar content, when epinephrine was administered. Loss of hepatic function in respect to the storage and mobilization of glycogen, which may be postulated in the cases of primary cancer of the liver with hypoglycemia reported by Nadler and Wolfer,[14] Crawford [15] and Beers and Morton [16] and in the cases of extensive fatty infiltration reported by Judd, Kepler and Rynearson,[17] may therefore be excluded. As to possible dysfunction of the adrenal glands, there had not been symptoms of adrenal insufficiency during life, and at necropsy the adrenal glands were perfectly normal morphologically. The other glands of internal secretion (the pituitary body was not examined) likewise appeared normal on microscopic examination.

It may be emphasized again that the tissue extracted and shown to contain insulin, just as in the case of Wilder, Allan, Power and Robertson, was metastatic island cell carcinoma from the liver, not tissue taken

14. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700-710 (Nov.) 1929.

15. Crawford, W. H.: Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, Am. J. M. Sc. **181**:496-502 (April) 1931.

16. Beers, D. N., and Morton, J. J.: Primary Carcinoma of the Liver with Hypoglycemia, Am. J. Cancer **24**:51-55 (May) 1935.

17. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Report of Two Cases Associated with Fatty Metamorphosis of the Liver, Am. J. Surg. **24**:345-363 (May) 1934.

directly from the pancreas. The quantity of insulin recovered in the extracts was rather small compared with the maximal yield from beef pancreas. In each instance, however, the tissues were frozen soon after death, thus inhibiting destruction of insulin, and the results obtained probably represent to a fair degree of accuracy the relative capacity of the metastatic tissue to produce insulin as compared with normal pancreatic tissue. Considering the large amount of metastatic tissue and the fact that its secretion, being released from neurogenic control, was probably continuous, there can be little doubt that the metastatic tumors may be held accountable for the hypoglycemia observed in this case and that this was a case of true hyperinsulinism.

The question as to whether malignant growths in general may contain extractable insulin-like substances deserves consideration. The literature on this subject up to 1927 (Wilder and others[2]) indicated that in all probability such is not the case, although there was one report to the effect that small amounts of insulin had been obtained from spindle cell sarcomas of rats (Roffo and Correa[18]). If at that time the criteria for proof of insulin activity, since enunciated by Best, Jephcott and Scott,[12] had been applied, it is possible that the outcome of the insulin assays might have been considered questionable. In the meantime the malignant tissue in two cases of primary carcinoma of the liver with hypoglycemia, those of Nadler and Wolfer[14] and Beers and Morton,[16] has been tested for the presence of insulin. The extracts were found to be inactive, whereas simultaneously prepared extracts of the pancreas, which was normal in both cases, contained insulin equivalent to a yield of about 100 units per kilogram. Although the patients in these two cases, and in a similar one described by Crawford,[15] required enormous amounts of carbohydrate to maintain a normal level for blood sugar, it does not seem probable that production of insulin was responsible for the hypoglycemia. Nadler and Wolfer stated, in addition, that the cancer cells in their case possessed none of the characteristics of islet cells.

SUMMARY AND CONCLUSIONS

A case of spontaneous hypoglycemia is described in which frequent feedings of carbohydrate were required to avert convulsions and coma. The liver appeared to function normally and to be able to release glycogen as dextrose when epinephrine was injected. At necropsy carcinoma of the islands of Langerhans was present, with multiple metastases, particularly to the liver. The cells of the metastatic nodules

18. Roffo, A. H., and Correa, L. M.: Presence in Malignant Growths of a Substance Resembling Insulin, Prensa méd. argent. **13**:668-669 (Dec. 20) 1926; abstr., J. A. M. A. **88**:767 (March 5) 1927.

in the liver closely resembled those of normal islands of Langerhans. This view was confirmed by the preparation from the hepatic nodules of an extract which contained insulin, a substance which, according to available evidence, is present in extractable amounts solely in cells of the islands of Langerhans. Classification of the condition as due to true hyperinsulinism seems justified.

This is the second case in which the presence of insulin in metastatic carcinoma of the islands of Langerhans has been demonstrated. The previous demonstration of this during study of a similar case by Wilder, Allan, Power and Robertson is fully confirmed, and the evidence is thus materially strengthened that metastatic carcinoma cells of the islands of Langerhans can retain the function of the parent cells.

MEDICINAL TREATMENT OF ANGINA PECTORIS

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Accurate evaluation of the efficacy of therapy in angina pectoris is difficult, for since cardiac pain is a subjective sensation with no constant outward manifestations, it is necessary to rely almost wholly on the patient's description of his symptoms. Variations in the physical and emotional activity of daily life, changes in the prevailing temperature and other factors difficult to evaluate cause changes in the frequency and severity of attacks of angina and make conclusions regarding therapeutic measures uncertain.

In a previous communication [1] it was shown that under standardized conditions a definite measurable amount of exercise will always induce a typical attack of angina in a given patient. This "standardized exercise tolerance test" has been used to measure objectively the therapeutic benefit derived from procedures such as total thyroidectomy [2] and to measure the heart rate and blood pressure during attacks of angina.[3] The present communication deals with its use in judging the therapeutic benefit derived from medicinal agents.

PLAN OF INVESTIGATION

Selection of Patients.—The subjects with angina pectoris selected for this study had symptoms corresponding to the syndrome described by Heberden.[4] All were ambulatory and, so far as could be determined, suffered from no illness other than

This investigation was aided by a grant from the DeLamar Mobile Research Fund.

From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine of the Harvard Medical School.

1. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients with Angina Pectoris on Exertion, Am. J. M. Sc. **188**:646, 1934.

2. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **52**:165 (Aug.) 1933.

3. Riseman, J. E. F.: The Relationship of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris on Exertion, Am. Heart J. **12**:53, 1936.

4. Heberden, W.: Commentaries, M. Tr. Coll. Physicians, London **2**:59, 1768.

disease of the coronary arteries. Patients with financial, domestic or social difficulties which were important factors in precipitating attacks were not included in this series. No patient was accepted for treatment who had experienced coronary occlusion within six months, and no patient was included in the final series unless his reaction to at least five different drugs had been studied. The periods of observation ranged from three to thirty-six months.

Of the twenty-six patients studied, twenty-one were men and five women. One patient was 38, four patients were from 47 to 49, sixteen were from 50 to 59, four were from 60 to 66 and 1 patient was 72 years of age. Thirteen had hypertension (a systolic blood pressure of 160 mm. of mercury or higher or a diastolic blood pressure of 100 mm. or higher). Roentgenograms taken at a distance of 7 feet (215 cm.) showed an enlarged cardiac shadow in eight patients. Electrocardiographic tracings showed changes consistent with disease of the coronary arteries in fifteen.

No attempt was made to alter the patients' mode of living in any way. Eight patients were unable to work because of their illness, fourteen were able to perform light work or housework in spite of attacks of pain and the remaining four worked full time.

All twenty-six patients experienced angina on exertion; this was confirmed by observation under standard conditions. Twenty gave a history of attacks also under emotional stress, eight experienced paroxysms also while at rest and seven occasionally had pain during sleep. The frequency of attacks under ordinary conditions of daily life varied considerably. One patient suffered from fifty to one hundred attacks every week, eleven patients stated that occasionally a week or ten days would elapse without cardiac pain while the remaining fourteen patients usually had at least one attack every day.

Method of Study.—To evaluate the severity of the condition and to obtain specific criteria by which to gage the results of therapy, all patients were observed in a special clinic for from one month to one year before therapy was begun. Fifteen different drugs were used, and the effect of mixed therapy also was studied. Each drug was used by at least twenty different patients. The order of administration was different for each patient. The medicines were taken by mouth three or four times daily: on arising, after lunch, after the evening meal and (when given four times daily) before retiring. Glyceryl trinitrate, for reasons to be explained later, was given at hourly intervals throughout the day. The doses of digitalis were calculated so that the patient would receive his full requirement of digitalis (according to weight by the method of Eggleston [5]) in seven days. The doses of drugs other than digitalis were the same for all patients, being sufficiently large to be therapeutically effective without a high incidence of untoward results.

Each drug was administered for at least one week before an attempt was made to evaluate the results. Two observers independently examined each patient, one using the usual clinical methods and the other the standardized exercise tolerance test. The results were compared only after each observer had independently reached a decision regarding the effect of the drug.

When there was evidence that a drug had exerted a beneficial effect, the medication was discontinued, and an inert tablet of similar appearance was substituted. When the cardiac symptoms had returned to their usual severity, as judged by clinical criteria and by the exercise tolerance test, other drugs were tested, and

5. Eggleston, C.: Administration of Digitalis by the "Eggleston Method," J. A. M. A. **74**:733 (March 13) 1920.

at a later date the medication which had yielded a beneficial result was again administered, this time in a disguised form (sugar coated, in capsule or painted with tincture of cudbear).

Evaluation of the Results.—The effect of medication was judged clinically according to three criteria: (1) the patient's own estimation of the efficiency of the drug, (2) the actual number of attacks experienced or the actual number of tablets of glyceryl trinitrate required during the period of medication and (3) the occurrence of untoward or unexpected symptoms. The number of attacks experienced during the period of medication was compared with the clinical condition before therapy was started and with that of the period when inert medication was given. The physical and emotional activity during this period also was estimated and was taken into consideration when necessary in evaluating the results.

Objective evaluation of the results of therapy was obtained by the standardized exercise tolerance test.[1] The test was performed in a room in which the temperature was maintained between 45 and 55 F. All tests were performed at least one hour after a light breakfast was eaten and from one and one-half to two and one-half hours after medication was received. In several instances tests were performed at different intervals after the drug was taken, in order to determine how soon it began to act and how long the action continued. Only one test was performed on a single day, and no test was performed if the patient had experienced an attack within one hour prior to his appearance at the clinic. The exercise consisted of repeatedly mounting and descending a two step staircase until precordial pain or discomfort developed. No untoward effects were experienced from this task, the angina subsided shortly after the work was stopped and in no instance was the precordial pain more severe than that experienced in daily life. No attempt was made to influence the rate of exercise, since patients will perform customary exertion, such as climbing stairs, at a fairly constant rate, and any attempt to influence the rate of exertion is usually followed by a change in exercise tolerance.[1] The exercise tolerance, according to this method, is the number of trips required to induce a typical attack of anginal pain. A single trip consists of one ascent and one descent of the staircase. The exercise tolerance of each patient was determined by at least three tests before medication was begun.

Under these constant conditions of exercise, temperature, food and emotional state, patients with angina have typical attacks after fixed amounts of exercise, even though intervals of several months separate the tests. This is shown by experience in over fifteen hundred tests performed by over one hundred and fifty patients.[6].

RESULTS

Results Based on Clinical Evaluation Alone.—According to the patients' reports, lactose or sodium bicarbonate was beneficial as frequently as other drugs (chart 1). Close questioning, however, frequently revealed that essentially the same number of attacks was experienced during any given period. The improvement apparently consisted of a sense of well-being, induced not by specific medication but by the fact that medical supervision was being given. Nine of twenty-one patients felt that they had been helped by the first few medications. Several felt better with every drug administered.

6. Riseman, J. E. F., and Brown, M. G.: Unpublished data.

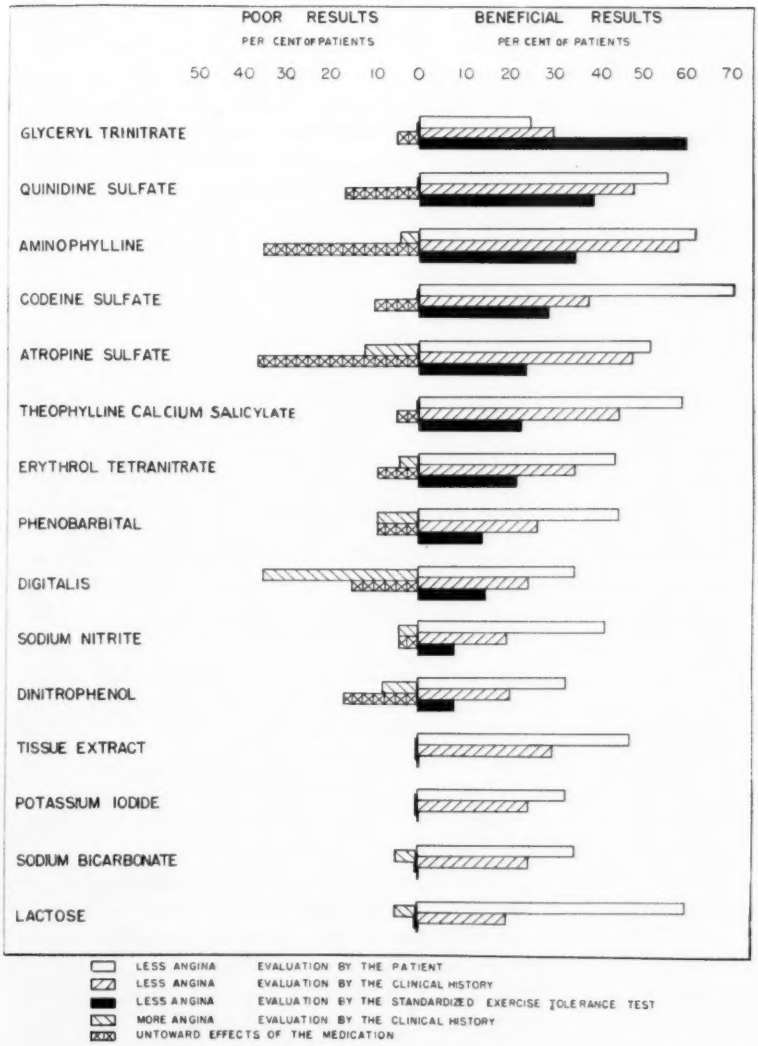

Chart 1.—The frequency of response of angina pectoris to medicinal treatment.

Determination of the actual number of attacks experienced during a given period of medication (or determination of the number of glyceryl trinitrate tablets used) suggested that sodium bicarbonate and lactose pills were of benefit in about a fifth of the patients, whereas aminophylline, quinidine sulfate and atropine sulfate helped approximately half the patients (chart 1). The clinical histories revealed that many patients, even without medication, occasionally experienced intervals of a week or more when they were comparatively free from cardiac pain. Furthermore, during periods of unemployment or warm weather a diminution in the frequency of attacks often occurred. Under such conditions it is obviously impossible to estimate how much of the apparent improvement was due to medication.

Results Based on the Standardized Exercise Tolerance Test Alone.—No patient was able to perform more work after taking lactose or sodium bicarbonate; furthermore, when some other medicine had been of benefit, the improvement always disappeared when the patient was given one of these two drugs. When the administration of a drug resulted in an increased ability to work, repetition of the period of medication practically always resulted in the same increase in exercise tolerance. With few exceptions, patients who showed an increase in exercise tolerance of at least 20 per cent experienced a diminution in the frequency of attacks in daily life. It is evident that clinical evaluation alone indicated improvement more frequently than actually occurred. The standardized exercise tolerance test, therefore, serves as a valuable check on the efficacy of therapy.

Evaluation of Results by Both the Clinical History and the Exercise Tolerance Test.—Improvement due to medication indicates that the patient reported he had been benefited by the drug, there was a decrease in the frequency of attacks in daily life and there was a definite increase in exercise tolerance. Furthermore, these indications of improvement disappeared when inert medication was given and reappeared in the same degree each time the specific medication was readministered.

The different drugs varied in their efficacy, and the different patients varied in their reaction to medication. Nine of the twenty-six patients (35 per cent) were not helped by any of fifteen different drugs. One patient responded to eight different medicines, fifteen were helped by from two to six drugs while the remaining patient responded to one of five drugs.

Inert Medication (pink lactose tablets four times daily; tablets of sodium bicarbonate, 5 or 10 grains [0.3 to 0.65 Gm.] three or four times daily).—Each of these two different types of inert medicament was given to twenty different patients. Seven patients believed that they were helped by sodium bicarbonate; five reported a diminution in the fre-

quency of attacks (chart 1). Twelve believed that the lactose tablets had been of value, four of these reporting that they had less pain while taking the tablets (chart 1). In no instance was the use of either of these drugs attended by an observable ability to perform an increased amount of work (charts 1 and 2).

Five patients believed the inert medicament had made them worse; however, the exercise tolerance remained unchanged, and the history revealed that they had had similarly poor weeks before medication was started. The increase in symptoms was probably due to contrast, for the inert drug was given after the use of beneficial medicament. Neither

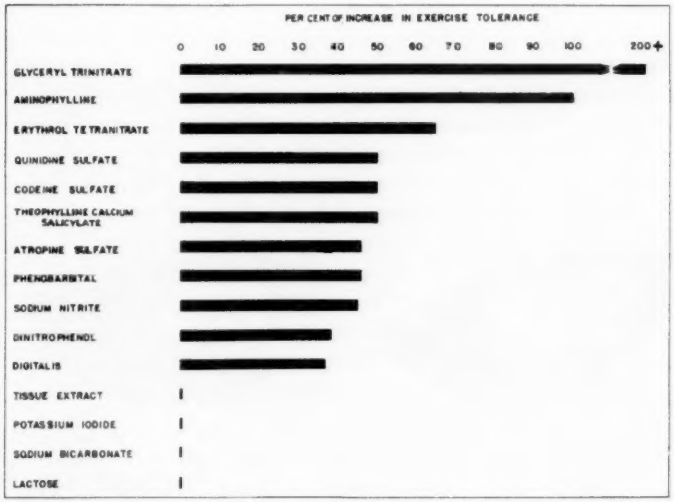

Chart 2.—The increase in the amount of work possible without pain after medicinal therapy.

sodium bicarbonate nor lactose was followed by any untoward symptoms, although one patient complained of cough and another of headache, which they attributed to the medication.

Potassium Iodide (10 grains [0.65 Gm.] three times daily) *and Tissue Extract* (1 tablet orally three times daily for at least three weeks).—The results with these drugs were similar to those obtained with lactose and sodium bicarbonate (charts 1 and 2). Potassium iodide was used by twenty-four and tissue extract by twenty patients. One patient had no attacks clinically during the three weeks that he took tissue extract, and his exercise tolerance increased from thirty-five to seventy-six trips. Repetition of the medication on two other occasions failed to show any

improvement; the first result in all probability was due to spontaneous variation in the course of the disease.

No untoward effects were observed in patients who took tissue extract. One patient showed marked swelling of the submaxillary glands every time potassium iodide was administered.

Glyceryl Trinitrate (1/500, 1/200 and 1/100 grain [0.1, 0.3 and 0.6 mg.] at intervals throughout the day).—In order to determine the duration of action of this drug the exercise tolerance was determined at varying intervals after a tablet of glyceryl trinitrate had been placed under the tongue. Especially prepared tablets containing 1/500 grain (0.1 mg.) of glyceryl trinitrate were employed, and the results were checked by the use of stronger doses. Only one of twenty patients experienced slight flushing and a slightly uncomfortable sense of fulness

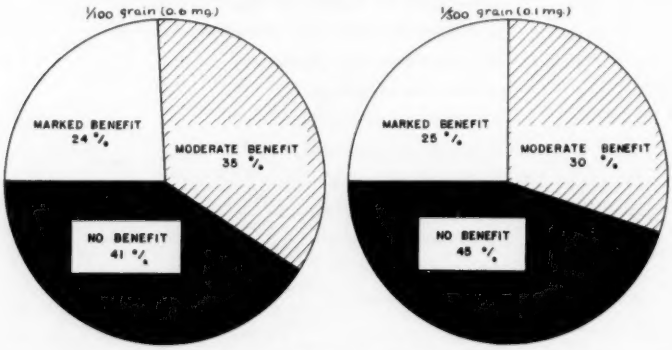

Chart 3.—The proportion of patients helped by glyceryl trinitrate given to prevent angina. The increase in exercise tolerance is shown as follows: The white area indicates 100 + per cent for thirty minutes; the shaded area, 100 per cent for from five to fifteen minutes, and the black area, no increase.

in the head after taking the smaller dose, whereas eleven of seventeen patients who received 1/100 grain (0.6 mg.) of glyceryl trinitrate complained of severe headache or other unpleasant symptoms.

The maximum prophylactic effect was evident about two minutes after the drug was taken. The duration and the degree of therapeutic effect varied in the twenty patients studied (chart 3). Five patients who without medication had angina after approximately thirty-five trips were able to undertake as many as one hundred trips without pain two minutes after taking 1/500 grain (0.1 mg.) of glyceryl trinitrate. This effect continued for approximately ten or fifteen minutes and then gradually diminished but did not disappear entirely for from thirty to sixty minutes. The therapeutic effect of 1/100 grain (0.6 mg.) of glyceryl trinitrate was even more prolonged—as long as seventy-five

minutes in one case (chart 4). Four of these five patients were completely free from anginal attacks in daily life when they took 1/500 grain (0.1 mg.) of glyceryl trinitrate at hourly intervals throughout the day. One of these patients was able to perform heavy work in a shipyard. The fifth patient was the one who was made slightly uncomfortable by even 1/500 grain (0.1 mg.), and it was inadvisable to use it clinically.

Six patients showed a moderately favorable response. After taking 1/500 grain (0.1 mg.) of glyceryl trinitrate they could do approximately twice as much work, and the attacks were of shorter duration and less severe. Five or ten minutes after the drug was taken, however, the exercise tolerance was the same as before (chart 5). These patients

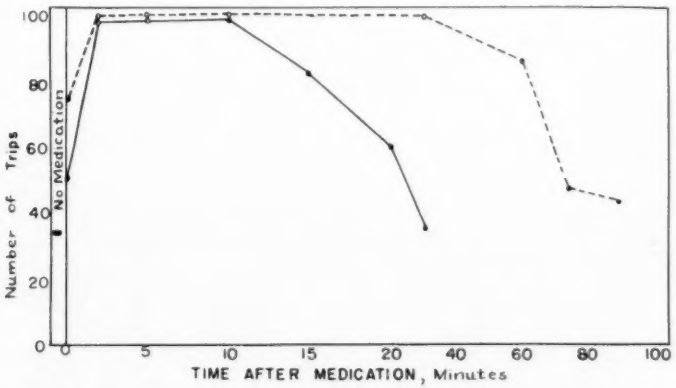

Chart 4.—The exercise tolerance of patient M. L. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day). This patient showed a marked response to the drug. In charts 4 to 6 a black circle indicates an anginal attack; a white circle, no attack; a solid line, 1/500 grain (0.1 mg.) of glyceryl trinitrate, and a dash line, 1/100 grain (0.6 mg.) of glyceryl trinitrate.

secured considerable relief from pain by taking 1/500 grain before going out into the cold or before undertaking undue exertion. This protection was of relatively short duration, and administration of the drug at hourly intervals did not render the patients completely free from attacks in daily life. The effect of 1/100 grain (0.6 mg.) was more lasting (about five minutes longer), but for all practical purposes the smaller doses were equally satisfactory.

In the remaining nine patients the ability to perform work was not influenced by glyceryl trinitrate (chart 6), and these persons observed no changes in their clinical condition when taking glyceryl trinitrate throughout the day or before performing any unusual exercise.

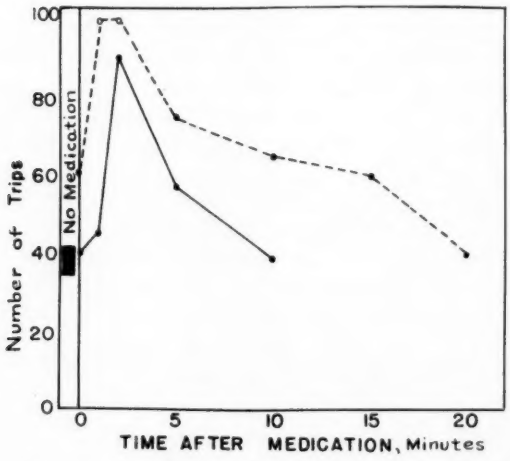

Chart 5.—The exercise tolerance of patient E. Ar. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day). This patient showed a moderate response to the drug.

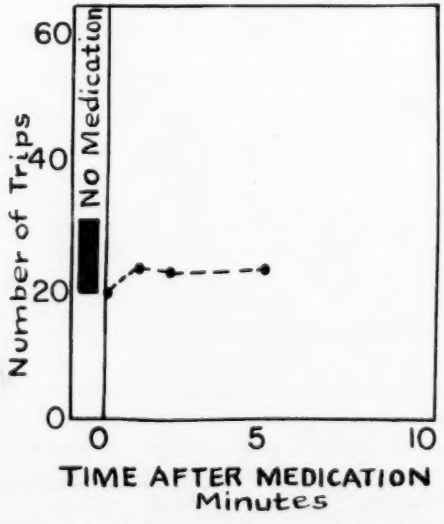

Chart 6.—The exercise tolerance of patient L. C. at different intervals after taking glyceryl trinitrate (only one test was performed on a given day). This patient showed no response to the drug.

Aminophylline (3 grains [0.2 Gm.] four times daily).—This drug was used by all twenty-six patients, nine of whom showed clinical improvement and an increased ability to work (chart 1). The increase in exercise tolerance following the use of this drug varied from 24 to 100 per cent (chart 2). Three other patients showed a 13 to 17 per cent increase in exercise tolerance but no change in clinical frequency of attacks.

Nine of the twenty-six patients had nausea or gastric distress when taking 3 grains (0.2 Gm.) of aminophylline (chart 1). In only one instance was this so severe that the medication had to be discontinued; in other instances the distress could be decreased by giving the pills together with sodium bicarbonate. Smaller doses (1½ grains [0.1 Gm.] three or four times daily) gave less gastric discomfort but failed to give satisfactory therapeutic benefit.

Quinidine Sulfate (5 grains [0.3 Gm.] four times daily).—Nine of twenty-three patients showed an increase in exercise tolerance of from 23 to 50 per cent (chart 2) after taking this medicament (chart 1). Three other patients showed from 14 to 19 per cent increase but no satisfactory clinical response. Three patients who failed to show any response to other medication did not receive quinidine.

Slight untoward effects were experienced by four patients. In one patient dermatitis developed and disappeared when the drug was withdrawn. The other three complained of diarrhea, which diminished when the dose of the drug was decreased to 3 grains (0.2 Gm.) four times daily; the therapeutic effect also was lessened with the smaller dose.

Atropine Sulfate (1/120 grain [0.5 mg.] four times daily).—Administration of this drug was followed in six of twenty-five cases by an increased ability to work (chart 1). The increase in exercise tolerance varied from 25 to 46 per cent (chart 2). Four of these patients showed a satisfactory clinical response, and one was helped by this medicament but not by quinidine or aminophylline. After the use of atropine one patient had a complete remission of symptoms both by clinical history and by exercise tolerance test on three distinct occasions separated by intervals of several months; the duration of the remission was at least two months. This patient showed a striking response to other drugs also, especially phenobarbital.

Unpleasant effects, especially dryness of the mouth, were experienced by nine patients (chart 1); in most instances the discomfort was severe. Several patients experienced more attacks while taking atropine (chart 1), possibly because of the discomfort caused by the drug. Two patients refused to continue the medication.

Three patients who experienced no relief from oral therapy were given the drug hypodermically in order to assure absorption. The

exercise tolerance was determined shortly thereafter, when signs of the effect of atropine, such as dryness of the mouth and blurring of vision, were evident. On successive days the dose was increased gradually from 1/120 to 1/60 grain (0.5 to 1.1 mg.). No change in exercise tolerance ensued.

Digitalis.—Twenty patients were given sufficient digitalis in the course of a week to approximate their full requirements. Three patients showed a slight but definite increase in ability to perform work (22 to 33 per cent increase in exercise tolerance) and a definite diminution in the frequency of attacks during daily life (charts 1 and 2). These patients were benefited by aminophylline also.

TABLE 1.—*Summary of Results Obtained in the Treatment of Angina Pectoris with Codeine Sulfate, Theophylline Calcium Salicylate, Erythrol Tetranitrate, Phenobarbital, Sodium Nitrite and Dinitrophenol*

	Number of Patients Studied	Patients Improved		Unpleasant or Toxic Effects	
		Number	Percentage	Number of Patients	Symptoms
Codeine sulfate, ½ grain (0.03 Gm.) four times daily	21	6	26	2	Obstipation
Theophylline calcium salicylate, 4 grains (0.26 Gm.) four times daily	22	5	23	1	Moderate gastric distress
Erythrol tetranitrate, ¼ grain 0.016 Gm.)* four times daily	23	5	22	2	Headache
Phenobarbital, ½ grain (0.03 Gm.) four times daily	22	3	14	2	Drowsiness
Sodium nitrite, 1 grain (0.065 Gm.) four times daily	26	2	8	1	Slight headache
Dinitrophenol, 5/12 grain (0.027 Gm.) four times daily	24	2	8	3	Nausea, tinnitus, loss of weight

* Larger doses were tried but had to be discontinued because of severe headaches.

The most striking effect of digitalis was an increase in the frequency and severity of the attacks of cardiac pain in daily life in seven patients, five of whom showed almost continuous angina (chart 1). The attacks became so frequent and so severe that it was deemed inadvisable to determine the exercise tolerance except for one patient, who showed a decrease of 21 per cent.

Other Substances.—The results obtained with codeine sulfate, theophylline calcium salicylate, erythrol tetranitrate, phenobarbital, sodium nitrite and dinitrophenol are summarized in table 1 and charts 1 and 2. No further comment is needed at this point.

COMMENT

Evaluation of Methods.—The clinical history elicits information as to the number and frequency of attacks experienced under the conditions of daily life and the patient's impression regarding the efficacy of treat-

ment. The exercise tolerance test measures under controlled conditions the effect of the drug in preventing the onset of an attack and indicates the rôle played by medication in bringing about improvement. It is necessary to combine the information obtained from both these sources in order to obtain an accurate picture of the response to therapy.

The unchecked clinical evaluation indicates that excellent results can be obtained in some cases from any form of medicinal therapy, including drugs which are inert. Evans and Hoyle [7] found that "a measure of improvement appears to result from every remedy tried, and at least as great an improvement during treatment with placebo." The experience of Master [8] and our own results judged solely on clinical data agree closely with those of the English investigators. This apparent improvement is probably due in large measure to the alleviation of anxiety. The problem is complicated further by the inability of the patient and doctor to differentiate between actual improvement brought about by medication and a decrease in symptoms due to variations in daily activity or spontaneous variations in the natural history of the disease.

If medication induces improvement in a patient who has attacks on exertion, this improvement should be evidenced by an ability to perform more work than was possible without medication.

The standardized exercise tolerance test duplicates the stimuli and environment which precipitate the majority of attacks in daily life, and, as far as can be determined, the attacks induced are similar to those experienced in normal life. In the absence of medication the amount of work which patients can perform before pain develops is extraordinarily constant under the standardized conditions employed in this study. Any change in exercise tolerance which regularly appeared after a given medication and which disappeared when the medication was omitted must have been caused by the drug.

An increase in exercise tolerance was rarely observed without clinical improvement. When the patient was able to exercise to the point of fatigue without pain, attacks in daily life were generally absent. Likewise, when an increased tolerance to exercise of from 50 to 75 per cent was present, the patient usually experienced fewer attacks. When an increase in exercise tolerance of less than 20 per cent was present, any apparent improvement was probably not related to treatment.

In order to make the results of this investigation directly applicable to the treatment of patients with angina in clinical practice, the method

7. Evans, W., and Hoyle, C.: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, Quart. J. Med. **2**:311, 1933.

8. Master, A. M.: Treatment of Coronary Thrombosis and Angina Pectoris, M. Clin. North America **19**:873, 1935.

of administering the drugs has been similar to that employed in general practice. No attempt has been made in this study to determine the influence of prolonged medicinal therapy. The course of the disease is so variable over long periods that it is almost impossible to differentiate between improvement due to prolonged therapy and spontaneous improvement brought about by time.

Value of Medication.—The doses of lactose and sodium bicarbonate used in these studies could not conceivably have had any direct influence on cardiac pain. The excellent clinical results obtained with these inert drugs, by others [9] as well as by ourselves, should make one skeptical of therapeutic claims based on clinical evaluation alone.

Potassium iodide has been used for generations in a number of different conditions. While of undoubted value in the treatment of cardiac pain due to syphilitic heart disease, it evidently has no place in the treatment of Heberden's angina.

Tissue extract is a more recent addition to medicine. Rumors as to its clinical effectiveness in angina have been frequent since its introduction by Schwartzman [10] in 1929. We have found no objective evidence that tissue extract administered orally is of value in treating cardiac pain.

The use of glyceryl trinitrate to decrease the duration of an attack is well recognized. The prophylactic value of the drug has received insufficient attention. Murrell's [11] original communication advocated the administration of glyceryl trinitrate several times a day in order to prevent attacks. More recently it has been suggested that it be used immediately before exertion is undertaken.[12] The present communication offers objective illustration of the value of these methods.

Approximately one third of the patients can be rendered completely free from attacks by taking 1/500 grain (0.1 mg.) of glyceryl trinitrate under the tongue at hourly intervals during the day. In approximately another third the beneficial effect is of only a few minutes' duration; such patients can secure considerable temporary relief by using the drug before any undue exertion or emotional strain. The remaining group of patients show no increase in ability to perform work after taking glyceryl trinitrate, or in fact any drug. It is important to realize that for all practical purposes small doses (1/500 grain) are as effective in preventing attacks as are larger doses and are attended by much less risk of inducing uncomfortable or harmful side-reactions.

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9. Evans and Hoyle.[7] Master.[8]

10. Schwartzman, M. S.: Ein neuer Weg in der Therapie der Angina pectoris, München. med. Wchnschr. **76**:1329, 1929.

11. Murrell, W.: Nitroglycerine as a Remedy for Angina Pectoris, Lancet **1**:80, 1879.

12. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

Aminophylline was introduced by Dessauer [13] as a readily soluble preparation of theophylline. Musser [14] and Gilbert and Kerr [15] have advocated its use in angina pectoris. When used in adequate doses the drug is frequently of undoubted benefit. It should be emphasized that a dose of less than 3 grains (0.2 Gm.) is of little value. The untoward effects in our experience are slight and offer little drawback to its clinical use.

The use of quinidine sulfate in the treatment of angina pectoris was recommended by Proger, Minnich and Magendantz.[16] These authors said they felt that it was of value for those patients whose heart rate failed to increase sufficiently during exercise or who showed extra systoles on exertion. Wayne and Graybiel [17] used the drug with success for a patient with ventricular fibrillation and angina sine dolore. We have found no correlation between the efficacy of quinidine sulfate in angina pectoris and the heart rate or rhythm during exertion. Furthermore, quinidine has been of distinct value for patients who have cardiac pain while at rest or when in bed.

Our use of quinidine sulfate was attended by no significant untoward effects; it is realized, however, that an occasional patient may be hypersensitive or show an idiosyncrasy to this drug.

Nine patients were given aminophylline and quinidine sulfate simultaneously (table 2). The combination was rarely of greater value than either drug given alone.

Codeine sulfate is clearly of value in the treatment of cardiac pain, but like other opium derivatives it is unsuited for prolonged use. If the relief which narcotics afford were caused by the analgesic action alone, it would be possible theoretically for a patient to continue exercising without pain until other, more serious consequences of myocardial anoxemia developed. The duration, severity and other characteristics of the attacks experienced after codeine sulfate was administered differed in no way from those when the patient was not taking the medicament, and there were no untoward effects. Possibly codeine acts to depress the patient's sensitivity to emotional reactions in general, thus

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13. Dessauer, P.: Euphyllin, ein neues Diuretikum, Therap. Monatschr. **22**: 401, 1908.

14. Musser, J. H.: Theophylline-Ethylenediamine in Heart Disease Associated with Pain, J. A. M. A. **91**:1242 (Oct. 27) 1928.

15. Gilbert, N. C., and Kerr, J. A.: Clinical Results in Treatment of Angina Pectoris with Purine Base Diuretics, J. A. M. A. **92**:201 (Jan. 19) 1929.

16. Proger, S. H.; Minnich, W. R., and Magendantz, H.: The Circulatory Response to Exercise in Patients with Angina Pectoris, Am. Heart J. **10**:511, 1935.

17. Wayne, E. J., and Graybiel, A.: Observations on the Effect of Food, Gastric Distension, External Temperature, and Repeated Exercise on Angina of Effort, with a Note on Angina Sine Dolore, Clin. Sc. **1**:287, 1934.

eliminating one stimulus which might induce pain or make it more easy for attacks to be produced by other stimuli, such as exertion.

Physicians frequently prescribe phenobarbital, yet there is little evidence that this drug causes an actual decrease in cardiac pain. Nine of twenty-two patients, however, volunteered the information that they experienced a sense of well-being while taking phenobarbital entirely different from that noted with any other form of medication. As one patient expressed it, "It made the pain easier to bear."

Phenobarbital, like codeine, probably renders the patient less sensitive to emotional stimuli and may also lessen the rate at which exercise is undertaken in daily life. This is illustrated by one patient who showed striking clinical improvement and was able to perform more work before pain developed after having secured a good night's sleep with the aid

TABLE 2.—*Comparison of the Exercise Tolerance After Aminophylline, Quinidine Sulfate and a Combination of the Two Drugs*

Patient	No. of Trips			
	No Medication	Aminophylline*	Quinidine Sulfate†	Aminophylline* and Quinidine Sulfate†
D. C.	20-32	29	23	23
P. R.	26-40	23	18	18
Y. E.	12-23	16	30‡	33‡
H. Sr.	26-31	22	38	34
H. S.	30-44	54	66‡	64
M. L.	33-34	57	34	50
E. A.	34-42	35	50	48
B. L.	8-11	10	10	16
S. R.	31-40	44	40	60

* Three grains (0.2 Gm.) four times daily.
† Five grains (0.3 Gm.) four times daily.
‡ No attack was induced by exercise.

of a single dose of 1½ grains (0.1 Gm.) of phenobarbital before retiring. The comforting effect of a good night's sleep apparently rendered this patient less sensitive to other stimuli during the day and so freed him from pain to a considerable degree. The effect of combining sedatives with other drugs deserves further study.

It has been stated that atropine prevents angina,[18] makes it worse [19] and has no effect on the condition.[20] The present investigation shows that different patients react differently to the drug. It is apparently of

18. Allbutt, T. C.: Diseases of the Arteries, Including Angina Pectoris, London, Macmillan & Company, 1915. Goldhammer, S., and Scherf, D.: Electrokardiographische Untersuchungen bei Kranken mit Angina pectoris ("ambulatorischer" Typus), Ztschr. f. klin. Med. **122**:134, 1932.

19. (*a*) Scherf, D., and Schnabel, P.: Atropine bei Angina pectoris, Klin. Wchnschr. **13**:1397, 1934. (*b*) Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort, Clin. Sc. **1**:103, 1933.

20. Stevens, A. A.: Angina Pectoris and Allied Conditions, M. Clin. North America **1**:293, 1917.

clinical value in about one third of the cases. Unfortunately one cannot predict which patient will be helped by the drug. The clinical value is further diminished by the high frequency of unpleasant reactions. In order to obviate these untoward symptoms, two synthetic preparations (syntropan and novatropine) were used by three patients who were helped by atropine. No untoward effects were noted, but neither of these commercial preparations had the slightest beneficial effect on cardiac pain.

Coogan [21] had used theophylline calcium salicylate with good clinical response in six cases of angina. The two purine derivatives used in this study had approximately the same theophylline content; nevertheless, aminophylline afforded relief to a greater number of patients and to a greater degree. An occasional patient, however, responded to the calcium salt and not to the ethylene diamine mixture. There is some evidence [6] that a double dose (2 tablets four times daily) of theophylline calcium salicylate is of greater value than the single dose; however, the cost of the drug at the present time practically prohibits such use. Theophylline calcium salicylate caused less gastric distress, but the dose of aminophylline used did not cause sufficient discomfort to prevent its use in angina. The reasons for these differences in action are not clear at the present time.

Erythrol tetranitrate was introduced for the treatment of angina pectoris by Bradbury.[22] Both erythrol tetranitrate and aminophylline are vasodilators, and these drugs are effective for the same patients. Erythrol tetranitrate in small doses is less likely to be accompanied with untoward effects and may be more satisfactory for some patients.

The work of Gilbert and Fenn [23] indicated that digitalis decreases the coronary blood flow. These investigators found that this drug frequently caused an increase in the clinical frequency of attacks.[24] The results of the present investigations are in complete accord with this view. This deleterious effect, however, does not occur in every instance; in fact, some patients are helped by the use of the drug. One would expect a decrease in angina in some patients who also show congestive failure, for in such cases the administration of digitalis should improve the general circulation, including that of the heart. Because of the strikingly bad effect in a large percentage of patients, this drug should be used with great caution in angina pectoris.

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21. Coogan, T. J.: Some Clinical Observations on the Uses of Theophylline Calcium Salicylate, Tr. Am. Therap. Soc. **34**:137, 1934.

22. Bradbury, T. B.: Some New Vasodilators, Brit. M. J. **2**:1213, 1895.

23. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**:668 (Nov.) 1932.

24. Fenn, G. K., and Gilbert, N. C.: Anginal Pain as a Result of Digitalis Administration, J. A. M. A. **98**:99 (Jan. 9) 1932.

In an occasional patient sodium nitrite may be of distinct value. One patient, not included in the present series, became completely free from attacks both clinically and by exercise tests on each of three occasions when the drug was given. The remission continued for several months after the drug was discontinued. Such responses, however, are rare; and despite reference [25] to the use of sodium nitrite in the treatment of angina, there is little to indicate its use now that other more effective vasodilators are available.

Tainter and his co-workers [26] have reported disappearance of angina pectoris following the use of dinitrophenol. The optimum dose in our experience [6] for patients with angina pectoris was 100 mg. daily. In view of the frequency with which untoward effects were experienced with even such small doses, it appears inadvisable to use this drug in the treatment of cardiac pain.

The apparent clinical improvement which follows the use of any drug (including placebos) in angina pectoris led Evans and Hoyle [7] to conclude: "We have been unable to convince ourselves that any drug tested is worthy even of trial in the routine treatment of the disease." The work of Wayne and Laplace [19b] and the results of the present investigation indicate that after the administration of certain drugs there is a distinct increase in the amount of work which can be performed by patients with angina pectoris. The present investigation also indicates that several of these drugs are of distinct value in the treatment of angina.

A few patients may be rendered completely free from cardiac pain under ordinary conditions of living as long as they continue taking effective medication. Occasionally these remissions continue after the medicine has been omitted; such occurrences, however, are comparatively rare. The majority of patients experience fewer attacks after effective medication but are not completely free from pain. About one-third derive no benefit from any of the customary forms of medicinal therapy.

We have no adequate means at the present time of predicting which drug will benefit a given patient, or, in fact, whether the patient will respond to any medication in any degree. In our experience a satisfactory method for medicinal treatment of patients with frequent attacks of angina pectoris has been to administer small doses of glyceryl trinitrate at hourly intervals throughout the day and before any undue exertion. Frequently it is of value to combine this therapy with phenobarbital or codeine. Patients whose attacks are less frequent also may

25. Evans, W., and Hoyle, C.: The Prevention and Treatment of Individual Attacks of Angina Pectoris, Quart. J. Med. **3**:105, 1934. Hay, M.: Nitrite of Sodium in Treatment of Angina Pectoris, Practitioner **30**:179, 1883.

26. Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: Use of Dinitrophenol in Obesity and Related Conditions, J. A. M. A. **101**:1472 (Nov. 4) 1933.

benefit from this regimen. The use of adequate doses of aminophylline or quinidine, however, may obviate the necessity for frequent administration. These two drugs are of value for approximately one half of all patients and for most of those patients who derive benefit from any form of medication. Should these drugs fail to confer sufficient relief or should their use be attended by untoward effects, theophylline calcium salicylate, atropine sulfate or erythrol tetranitrate is worthy of trial before resort is made to surgical procedures (chart 7).

It is evident that the response to medication is no indication as to the prognosis for a given patient. In the present series of twenty-six patients, five experienced attacks of coronary occlusion, and one had congestive failure during the period of observation. Two of these patients died. All but one of these complications occurred at least one month after the patient had stopped all medicinal therapy and could

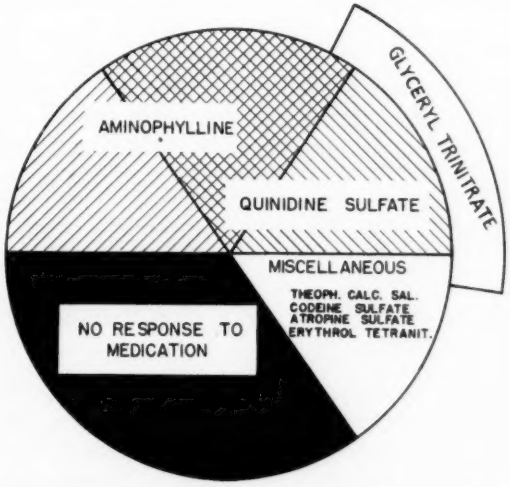

Chart 7.—The proportion of patients responding to medication.

in no way be attributed to the use of the medication or to the exercise tolerance test. In the remaining patient coronary occlusion developed during the week that he was taking glyceryl trinitrate as a prophylactic against attacks. Three of these patients had shown striking clinical benefit following several different types of medication; the remaining three had shown no response to any of the fifteen drugs.

It is to be remembered that drug therapy is only one factor in the medical management of angina pectoris. In many instances beneficial adjustments can be made in the patient's mode of living, while in other instances the correction of anemia, hyperthyroidism or other physical ailments may be of importance.

SUMMARY AND CONCLUSIONS

The use of fifteen different drugs in the treatment of twenty-six patients with angina pectoris was studied. Each drug was given several times a day for at least a week before its effect was evaluated. The efficacy of treatment was ascertained by the usual clinical methods and also by determining how much work, under standardized conditions, the patient could perform before pain developed. Control observations were made to differentiate between spontaneous remissions and improvement due to treatment.

The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value. Placebos were just as often beneficial as other medicaments.

The exercise tolerance test revealed that patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide or tissue extract were unable to perform any more work than was possible without medication.

Glyceryl trinitrate given before work was undertaken prevented attacks and enabled many patients to do considerably more work. This prophylactic effect was often of relatively short duration, but attacks were prevented for as long as an hour in many cases. Such patients could be rendered completely free from attacks in daily life by taking glyceryl trinitrate at hourly intervals. For all practical purposes small doses (1/500 grain, or 0.1 mg.) were as valuable as larger doses and were attended by little discomfort.

One half of the patients were benefited by either aminophylline or quinidine sulfate. Aminophylline had to be given in doses of 3 grains (0.2 Gm.) to be effective.

Theophylline calcium salicylate, erythrol tetranitrate and atropine sulfate were often of value; occasionally they benefited patients not helped by either aminophylline or quinidine sulfate. The doses of atropine necessary frequently caused discomfort because of side-reactions.

Codeine sulfate and phenobarbital rarely enabled the patient to do more work before pain developed, but these sedatives appeared to be of aid as an adjunct in the treatment of the patient.

Sodium nitrite and small doses of dinitrophenol were only rarely of benefit. Other more effective drugs are available, and dinitrophenol, even in the small doses used, occasionally gave undesirable side-reactions.

Digitalis was rarely of value and frequently caused a striking increase in anginal attacks.

The following pharmaceutic houses supplied the products used in this investigation: Bilhuber-Knoll Corporation, theophylline calcium salicylate; Burroughs Wellcome & Co., erythrol tetranitrate, and Winthrop Chemical Co., Inc., tissue extract.

NORMOGLYCEMIC GLYCOSURIA DIFFERENTIATED FROM OTHER BENIGN GLYCOSURIAS AND DIABETES MELLITUS

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This paper presents a review of 3 cases of glycosuria, which we have recently had the opportunity to study, in which the sugar content of the blood was normal. It was our feeling that attention should be called to the necessity of a complete investigation of all cases of glycosuria before the institution of the rigid management required by the diagnosis of diabetes mellitus. The social and financial implications of this disease are well realized even by one not in frequent contact with diabetic patients, and for these reasons alone the diagnosis should be made only after the most careful study and the accuracy of the diagnosis should be suspected if after a sufficient trial careful management is unsuccessful.

Of the nondiabetic glycosurias, that due to a lowered renal threshold for dextrose is the most common; the others, such as pentosuria, lactosuria, fructosuria and galactosuria, will be referred to only briefly.

REVIEW OF THE LITERATURE

Normoglycemic glycosuria is known in the clinical literature as renal diabetes, renal glycosuria, benign glycosuria and orthoglycosuria. Von Noorden [1] has used the term normoglycemic glycosuria and Hjärne [2] the term orthoglycosuria, and these are perhaps the ones of choice, as they describe this clinical entity without giving any misleading suggestion as to its pathologic nature. As the name implies, the condition is one in which sugar appears in the urine in amounts detectable by the usual qualitative tests while the sugar content of the blood does not rise above normal limits at any time. Though the renal

From the Department of Medicine of the University of Chicago.

1. von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927.

2. Hjärne, U.: A Study of Orthoglycaemic Glycosuria with Particular Reference to Its Hereditability, Acta med. Scandinav. **67**:422, 1927.

threshold is lowered for dextrose in this condition, no pathologic observations have yet been described which permit its diagnosis at autopsy.[3] The threshold may be lowered to a degree permitting constant glycosuria, called by Malmros[4] glycosuria innocens and by Holst[5] renal diabetes; or the glycosuria may occur only after meals, when the sugar content of the blood is elevated above the fasting level. To this these same authors have given the name cyclic glycosuria and cyclic renal glycosuria.

The literature indicates this condition to be rather rare. Fowler,[6] in his summary of cases at the Montreal General Hospital, stated that the incidence is 1.75 per thousand cases of glycosuria, and he quoted the incidence of the revised figures from Joslin's clinic as being 1.66 per thousand cases of glycosuria. There appears to be no particular age group in which a majority of these cases occur. In those reviewed by Marble[7] from Joslin's clinic the average age at the time of onset was 19.9 years. The youngest patient was reported on by Paullin and Bowcock, quoted by Fowler.[6] In this case glycosuria was discovered when the patient was 2 years of age and had been constantly present for twenty years since then. Younger patients in whom glycosuria has been discovered have been reported on, but the glycosuria was only transient. For a more complete bibliography of this subject the reader is referred to Marble's excellent paper on "Renal Glycosuria."

DIAGNOSTIC CRITERIA

The criteria for the diagnosis of normoglycemic glycosuria have been given by many authors and may be summarized as follows:

1. The reducing substance in the urine must be identified as dextrose. Pentosuria, lactosuria, fructosuria and galactosuria may occur; but unless dextrose is found in abnormal amounts without hyperglycemia, renal glycosuria is not present.

2. Glycosuria must occur without hyperglycemia and may be constant or may occur only during the postprandial period as a cyclic glycosuria.

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3. Fitz, R.: Renal Diabetes, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1931, vol. 4, pt. 1, p. 178 (13).

4. Malmros, H.: A Study of Glycosuria with Reference to the Interpretation of the Incidental Finding of a Positive Reduction Test, Acta med. Scandinav. supp. 27, 1928, p. 1.

5. Holst, J. E.: Investigations into Benign Glycosuria and Diabetes Mellitus, Acta med. Scandinav. **63**:47, 1925.

6. Fowler, A. F.: Renal Diabetes, Ann. Int. Med. **7**:518, 1933.

7. Marble, A.: Renal Glycosuria, Am. J. M. Sc. **183**:811, 1932.

3. The level of the sugar in the blood during fasting and the results of a standard dextrose tolerance test must be normal. This of course takes into consideration the effect of emotion or illness, which may greatly increase the blood sugar.

4. Symptoms suggestive of diabetes mellitus must be absent or explainable by some process such as hyperthyroidism, which may cause loss of weight, weakness and hunger.

5. There should be, ideally, no family history of diabetes mellitus. The history of glycosuria in the family, however, often aids in making the correct diagnosis, as the familial characteristic is common in renal glycosuria.[5]

6. There should be little or no relation between the intake and the excretion of sugar. This holds true for the case in which there is marked and constant glycosuria, but when the glycosuria is cyclic the excretion of sugar will follow to some extent the intake of sugar and the rate of absorption.

7. The rate of utilization of sugar should be normal. However, as has been pointed out by Rabinowitch [8] and Paullin,[9] persons with mild diabetes often show no changes in the respiratory quotient which would aid in differentiating them from nondiabetic persons.

8. The patient must not subsequently show diabetes. Rabinowitch [8] gave no time limit, but Joslin has fixed it at a maximum of three years from the time the diagnosis of renal glycosuria is made. It of course cannot be made too long, for every person has a chance of about 1 per cent that the disease will develop.

MATERIAL AND METHODS OF STUDY

Three patients were investigated because of continued glycosuria of varying degree with what seemed adequate diabetic management. One of the patients, who was being treated with insulin, continued to have marked glycosuria and at the same time to complain of insulin-like reactions. Single determinations of the sugar content of the blood during treatment for diabetes mellitus disclosed that symptoms of hypoglycemia occurred at times when there was definite hypoglycemia, and at no time was there found an abnormal sugar content, as might be expected in a case of diabetes mellitus with constant glycosuria. The other patients presented problems of a somewhat different nature. They apparently had mild diabetes, and the condition should have been satisfactorily controlled with diet therapy. Never had there been sufficient glycosuria to warrant the use of insulin for these middle-aged persons, and never had dietary shifts in the carbohydrate-fat ratio or in the total food content been sufficient to change markedly the degree of glycosuria.

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8. Rabinowitch, I. M.: The Diagnosis of Renal Glycosuria, Canad. M. A. J. **22**:329, 1930.

9. Paullin, J. E.: Glucose Utilization in Renal Glycosuria, Arch. Int. Med. **37**:88 (Jan.) 1926.

The methods of study used in making the differential diagnosis were those at hand in the nutrition laboratory,[10] namely, the determination of the dextrose content of capillary blood at frequent intervals, usually every fifteen minutes, for a period of from three to four hours after a dextrose test meal, the collection of urine at times corresponding to the capillary punctures and the identification and determination of the amounts of reducing substances present.

Analyses were made for capillary blood by the micromethod of Folin and Svedberg,[11] which is accurate for values ranging from 40 to 350 mg. per hundred cubic centimeters. One modification was added to this method by collecting and oxalating the blood in small funnels before samples were taken for analysis.

The urine was analyzed qualitatively by Benedict's alkaline copper solution and quantitatively by the method of Shaffer and Hartmann[12] when the qualitative tests of the specimens were positive for dextrose. Fermentation tests were used to identify the reducing substances. Each twenty-four hour specimen which the patient brought to the laboratory on the day of an examination was analyzed quantitatively.

The intake of food of each subject was weighed or measured for a long period prior to the study. The carbohydrate content was calculated, and known additions were made according to the method suggested by Woodyatt[13] for the diagnosis of latent or mild diabetes mellitus.

The dextrose test meal in each case consisted of 1 Gm. of dextrose per kilogram of standard body weight and was given in a solution made up to 400 cc. and flavored with lemon juice.

REPORT OF CASES

CASE 1.—In a 34 year old married woman glycosuria was found in 1922 during her stay in a hospital because of spontaneous abortion. After this discovery she was placed on a qualitatively restricted diet until the summer of 1933. Throughout this period there was a strong reduction of the urine at each analysis made by her physician, regardless of how severely the intake of carbohydrate had been restricted. During this period she noticed growing weakness, loss of weight and frequent boils. There was no polyuria or polyphagia. In the summer of 1933 she was given a diet of 70 Gm. of carbohydrate and 9 units of insulin twice daily, but even under this management the urine continued to show three and four plus reduction whenever tested. On her first visit to this clinic she complained of weakness and nervousness.

On physical examination at the time of her admission to the clinic, on Dec. 4, 1933, she was found to be a tired and nervous woman, measuring 165 cm. in height and weighing 56.1 Kg. The blood pressure was 110 systolic and 68

10. Laboratory of F. H. Smith in the Department of Medicine, the University of Chicago.

11. Folin, O., and Svedberg, A.: Micro Methods for the Determination of Non-Protein Nitrogen, Urea, Uric Acid, and Sugar in Unlaked Blood, J. Biol. Chem. **88**:85, 1930.

12. Shaffer, P. A., and Hartmann, A. F.: Methods for the Determination of Reducing Sugars in Blood, Urine, Milk and Other Solutions, J. Biol. Chem. **45**:365, 1921.

13. Woodyatt, R. T.: Some Milder Forms of Diabetes with Special Reference to Mild Diabetes in Elderly Persons with Arteriosclerosis, South. M. J. **17**:145, 1924.

diastolic. The thyroid gland was palpable, and a basal metabolism test made later showed a rate of + 15 per cent. Laboratory examination showed 4,080,000 red blood cells, 79 per cent hemoglobin and 6,500 white blood cells. The Wasser-

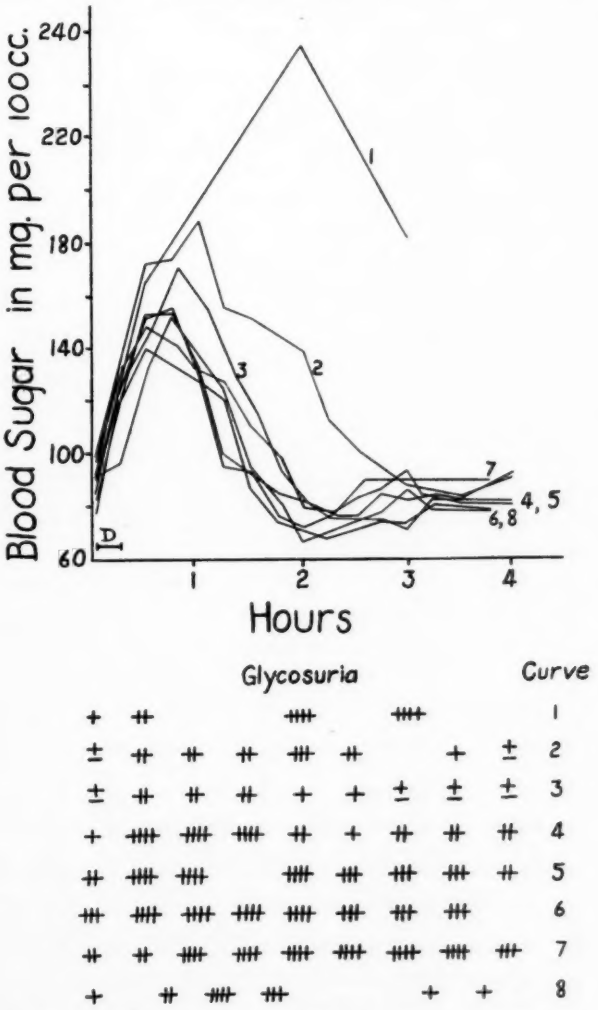


Fig. 1 (case 1).—Dextrose tolerance tests. *D* represents a dextrose meal of 50 Gm.

mann and Kahn tests were negative. Analysis of a single specimen of urine revealed a trace of sugar, while the twenty-four hour specimen which the patient brought in contained 7 Gm. of sugar and a trace of acetone. The sugar content of the blood during fasting was 92 mg. per hundred cubic centimeters.

On her second visit to the clinic the dextrose test meal was given, because the symptoms at the time suggested some atypical glycosuria. The results are shown in figure 1, curve 1. It was a typically diabetic curve, and a diagnosis of diabetes mellitus was made on its basis; insulin and diet therapy were continued as before. Table 1 is a brief of the metabolic study made in the outpatient department.

Ten months after this first dextrose tolerance test, studies of the blood sugar relative to the effect of exercise in diabetes mellitus were made for the patient. The results of these experiments are seen in figure 2. Examination of these curves for blood sugar showed that, with the exception of higher levels during

TABLE 1.—*Data for First Patient Obtained in Outpatient Department*

Date	Weight, Kg.	Urine, 24 Hr., Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Dextrose, Gm.	Insulin A.M.	Insulin Noon	Insulin P.M.	Comment
12/ 4/33	56.1	7.0	90	68	157	2,045	145	15	0	15	Trace of acetone; fasting blood sugar, 92 mg. per 100 cc.
12/11/33	55.0	20.9	80	62	146	1,882	131	15	5	10	Dextrose test meal, curve 1, fig. 1
12/21/33	53.9	6.7	90	68	157	2,045	145	10	5	10	Basal metabolic rate, +15%
12/29/33	....	....	90	68	157	2,045	145	10	5	10	Basal metabolic rate, +17%; compound solution of iodine, 5 drops, 3 times a day
1/12/34	54.1	Trace	90	68	157	2,045	145	10	5	10	Complaints of weakness
2/12/34	55.4	Trace	90	68	157	2,045	145	10	10	10	Complaints of weakness
3/26/34	54.5	15.0	90	68	186	2,306	148	10	10	10	Complaints of weakness
4/23/34	54.0	7.6	90	68	186	2,306	148	10	10	10	Complaints of weakness
5/21/34	53.6	Trace	90	68	186	2,306	148	10	10	10	Complaints of weakness
6/15/34	....	....	45	..	...	.....	45	25	30	16	Hospitalized for dilation and curettage; mild ketosis
7/ 9/34	50.8	1+	..	..	...	.....	...	10	10	10	

fasting, the curves were within normal limits. The finding of a constant and rather marked glycosuria at these normal levels for blood sugar led to a diagnosis of renal or normoglycemic glycosuria. At the time this study was made the patient was on a diet of 100 Gm. of carbohydrate, 72 Gm. of protein and 213 Gm. of fat. She was taking 10 units of insulin before breakfast, 10 units at noon and 10 units before the evening meal.

The day on which the last curve for blood sugar with exercise was made the patient entered the hospital so that a more complete analysis could be carried out and the possibility of well controlled diabetes mellitus accompanying the normoglycemic glycosuria could be investigated. The results of these tests are shown in figure 1. Table 2 gives a summary of the dietary changes and the amount of sugar found in the urine during the patient's stay in the hospital.

A diagnosis of uncomplicated normoglycemic glycosuria was made on Nov. 15, 1934, and the patient was asked to test the urine of her blood relatives. Her

mother and two sisters were found on several occasions to have postprandial glycosuria of one plus reduction. Further investigation would have been interesting but could not be carried out.

TABLE 2.—*Data for First Patient During Hospitalization*

		Urine, 24 Hr.			Diet					Blood Sugar, Mg. per 100 Cc.			
Date	Weight, Kg.	Gm.	Total Nitrogen, Gm.	Creatinine, Gm.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Dextrose, Gm.	8 A.M.	10 A.M.	Noon	Comment
11/ 6/34	....	4.7	9.36	1.13	100	72	213	2,605	162	...	...	..	Blood sugar curve 4, fig. 2; insulin, 0, 10, 0 units
11/ 7/34	....	11.1	10.50	1.22	100	72	213	2,605	162	...	...	..	No insulin
11/ 8/34	....	13.9	10.80	1.24	100	72	213	2,605	162	84	101	91	
11/ 9/34	....	13.1	11.73	1.17	100	72	213	2,605	162	102	95	90	
11/10/34	....	20.6	11.59	1.23	200	72	213	3,005	262	...	...	..	Dextrose test meal, fig. 1, curve 2
11/11/34	....	16.0	11.53	1.18	200	72	213	3,005	262	...	...	..	
11/12/34	....	17.5	11.26	1.18	200	72	213	3,005	262	94	93	88	
11/13/34	50.2	27.4	11.00	1.28	250	72	213	3,205	312	90	112	91	Basal metabolic rate, +12%
11/14/34	....	23.0	11.10	1.23	300	72	213	3,405	362	98	91	97	
11/15/34	....	21.0	11.55	1.30	300	72	213	3,405	362	100	95	95	Blood sugar at 9 a.m., 104 mg.; fig. 1, curve 3

TABLE 3.—*Data for First Patient Obtained Subsequently in Outpatient Department While on General Diet*

		Urine, 24 Hr.			
Date	Weight, Kg.	Dextrose, Gm.	Total Nitrogen, Gm.	Creatinine, Gm.	Comment
1/ 6/35	....	36.2	9.50	1.10	No ketosis
1/ 7/35	....	49.4	11.08	1.33	No ketosis
1/11/35	....	30.5	8.80	1.76	No ketosis
1/12/35	....	5.9 (4 hr.)	.....	....	Dextrose test meal, fig. 1, curve 4
2/17/35	....	19.3	9.64	1.68	4 month pregnancy, curve 5, fig. 1
2/18/35	53.6	22.4	8.12	1.76	No ketosis
4/14/35	58.4	51.0	11.14	1.09	No ketosis
4/15/35 4/16/35	....	55.0	11.42	0.90	No ketosis; dextrose test meal, fig. 1, curve 6
5/24/35	....	51.2	9.27	....	No ketosis
6/19/35	....	44.6	8.89	0.79	No ketosis
6/20/35	....	52.0	8.53	1.08	No ketosis
6/21/35	....	....	.....	....	Dextrose test meal, fig. 1, curve 7

Since her discharge from the hospital, on Nov. 15, 1934, the patient has been on a general diet, and table 3 is a brief of her frequent visits to the outpatient clinic.

It is interesting to note the increased glycosuria as the pregnancy, which was first diagnosed on Feb. 17, 1935, progressed. Several studies of the blood sugar and urine of the infant were made when she was 1 month old, both before and after feeding, but no abnormal values or glycosuria were found.

REPORT OF CASES

Snoeck [14] in a series of 2,200 cases of pregnancy found an incidence of 3 per cent for glycosuria and of 1 per cent for lactosuria. Ninety-

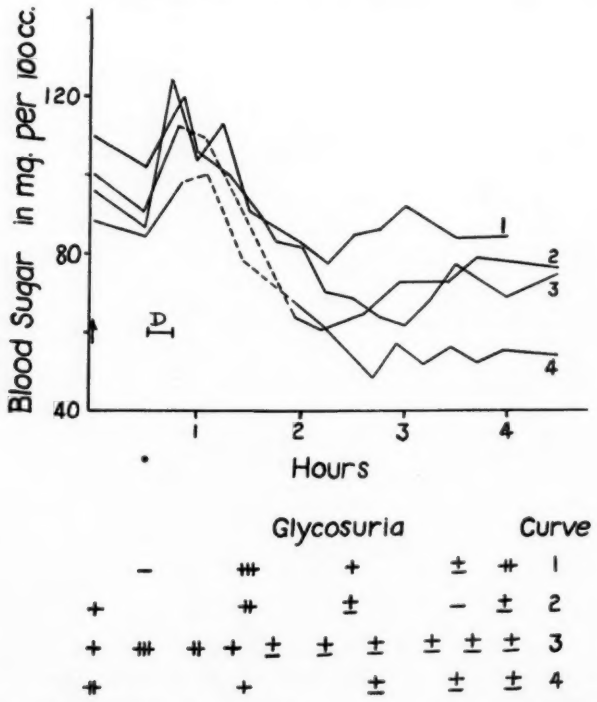


Fig. 2.—In figures 2 to 4 the solid line represents a period of rest and the dash line a period of work. For curve 2 there was 3,010 Kg. meters of work, and in curve 4 there was 3,275 Kg. meters. *D* represents a mixed meal of 32 Gm. of carbohydrate, 14 Gm. of protein and 56 Gm. of fat. The arrow indicates the administration of 10 units of insulin.

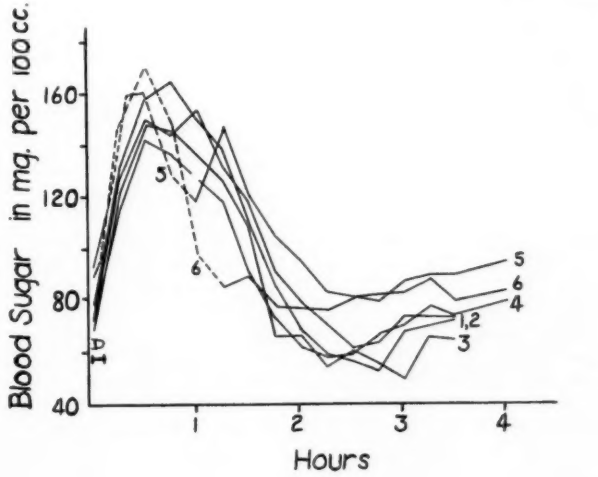
five per cent of the instances of glycosuria occurred in the latter half of pregnancy. Williams [15] in an earlier study found an incidence of

14. Snoeck, J. J.: Recherches sur la glycosurie et la lactosurie gravidiques, Arch. internat. de méd. expér. **7**:349, 1932.

15. Williams, J. T.: Some Observations upon the Glycosuria of Pregnancy, Boston M. & S. J. **192**:163, 1925.

13.6 per cent in the 500 pregnant women tested. The discrepancy probably occurred because Williams used the Fehling solution, which is more sensitive to the nonreducing substances than is the Benedict solution, which was used by Snoeck.

Case 2.—A 34 year old Jew had been observed in the clinic since October 1929. Glycosuria was discovered accidentally in 1921, and his diet was qualitatively restricted at this time; but glycosuria continued intermittently. In 1924 he had a



Glycosuria								Curve
−	±	+	±	−	−	−	−	1
−	+	+++	+	−	−	−	−	2
−	+	+++	++	−	−	−	−	3
−	+	++	−	−	−	−	−	4
−	±	+	+	−	−	−	−	5
−	±	+	+	−		−	−	6

Fig. 3.—Curve 5 represents 9,126 Kg. meters of work, and curve 6 represents 14,220 Kg. meters. *D* represents a dextrose meal of 66 Gm.

cholecystectomy and an appendectomy, and during his subsequent stay in the hospital traces of sugar were occasionally found in the urine. The values for blood sugar during fasting ranged from 77 to 90 mg. per hundred cubic centimeters. His diet was more rigidly restricted, but occasionally glycosuria was noted.

During 1929 he experienced epigastric distress, and after he was started on a modified Sippy diet, a dextrose tolerance test was given, with entirely normal results. He had experienced symptoms of hypoglycemia at the third hour. On a

second test during this same year hunger and dizziness were noted at the end of three hours. Forty-five minutes after the ingestion of dextrose for the third test the blood sugar content was 225 mg. per hundred cubic centimeters, but symptoms of hypoglycemia were again noted at the third hour.

When first seen at this clinic in 1929 he reported having occasional glycosuria, although he remained on a restricted diet.

On Oct. 1, 1929, the patient was found to measure 166.5 cm. in height and to weigh 63.1 Kg. There were no outstanding physical findings warranting mention. Laboratory analysis of the blood showed 5,360,000 red blood cells, 12,900 white blood cells, negative Wassermann and Kahn reactions and a fasting level for blood sugar of 88 mg. per hundred cubic centimeters. Urinalysis revealed no abnormality. Roentgen examination demonstrated either an ulcer in the base of the bulb involving the pylorus or extensive adhesions involving the entire pylorus and duodenum.

Until June 1931, when one twenty-four hour specimen of urine contained 12 Gm. of dextrose, the urine was free from reducing substances. In December 1934 the patient was placed on a general diet with feedings between meals. Urinalysis showed no sugar, and the fasting level for blood sugar was 68 mg. per hundred cubic centimeters.

In January 1935 further study was started in the nutrition laboratory, the results of which are shown in figure 3. The first five dextrose tolerance tests were made while the daily intake of food consisted of 170 Gm. of carbohydrate, 70 Gm. of protein and 120 Gm. of fat. The sixth test was made after a period of thirteen days during which there was a daily intake of 220 Gm. of carbohydrate, the protein and fat content remaining the same as for the other tests. This increase was made in order to expose mild diabetes mellitus by increasing the postprandial level of the blood sugar and glycosuria as compared with the blood sugar content and glycosuria on the lower intake of carbohydrate.

Case 3.—A 47 year old man was first seen on Jan. 19, 1932. His paternal grandmother was known to have had glycosuria, but other than that the family history was unconsequential.

In 1926 the patient weighed 93.5 Kg. and was refused life insurance because of hypertension. In 1931 he was found to have symptomless glycosuria and was placed on a qualitatively restricted diet.

On the first visit to the clinic the patient measured 168 cm. in height and weighed 77.4 Kg. Studies of the blood showed 5,080,000 red blood cells and negative Wassermann and Kahn tests. The blood pressure was 172 systolic and 130 diastolic. A single specimen of urine was negative for reducing substances. On two succeeding days twenty-four hour specimens of urine were free from sugar, and the fasting level for blood sugar for these two days was 55 and 68 mg., respectively, per hundred cubic centimeters.

There was no exact management for this patient, although he was started on a limited diet of 100 Gm. of carbohydrate, 60 Gm. of protein and 150 Gm. of fat for the first week. Within one month the diet was increased to 250 Gm. of carbohydrate, 60 Gm. of protein and 150 Gm. of fat and maintained for six months. Throughout this time the fasting level for blood sugar was normal, and analysis of twenty-four hour specimens of urine revealed no sugar. Eight months after the initial observation, a dextrose tolerance test was performed and gave normal results; nevertheless, the patient was advised to limit his diet in order to control his weight, which was now 80.1 Kg.

On Jan. 9, 1935, the patient was called to the nutrition laboratory for a recheck on the utilization of dextrose. At this time his average intake was approximately

170 Gm. of carbohydrate, 60 Gm. of protein and 55 Gm. of fat. With an intake of about 1,416 calories his weight was 81.3 Kg. A dextrose tolerance test made at this time is recorded in figure 4, curve 1. For six days following this test the patient's diet was increased to a carbohydrate intake of 290 Gm. per day by the addition of candy. A second dextrose tolerance test following this regimen is recorded in figure 4, curve 2. The diet was again increased, this time to 410 Gm. of carbohydrate, by the addition of candy. This diet was continued for five days, and a third dextrose tolerance test was then made (fig. 4, curve 3). The

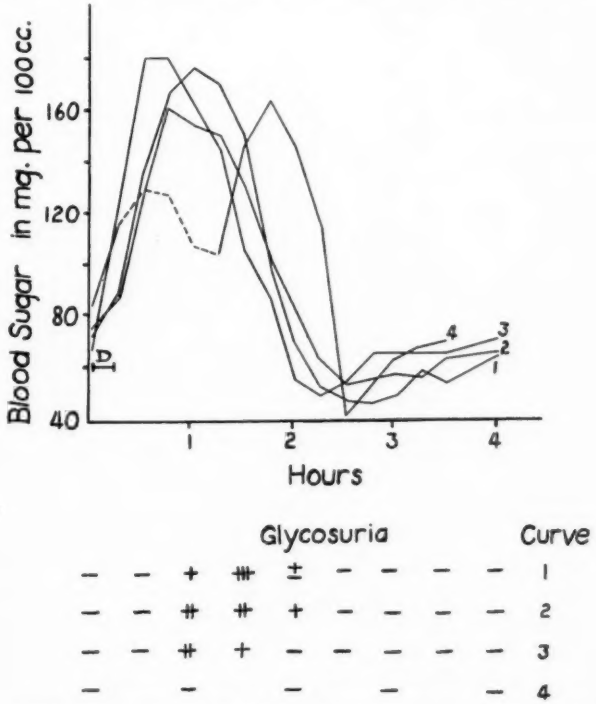


Fig. 4.—Curve 4 represents 10,850 Kg. meters of work. *D* represents a meal of 70 Gm. of dextrose.

diet was then reduced to the usual intake of 170 Gm. of carbohydrate per day to prevent a gain in weight, and the fourth test was made while the patient was on this diet.

RESULTS

The diagnosis of normoglycemic glycosuria was established in the first case by the findings for blood sugar and urinary sugar, as shown in figure 2. It is noted that insulin prevented the usual postprandial rise in the level for blood sugar, showing that insulin will lower the level for blood sugar in persons with renal glycosuria as it will in

normal persons. Powelson and Wilder [16] have used insulin to lower the level of the blood sugar in cases of normoglycemic glycosuria in which they wished to establish the absolute threshold for dextrose. In our case 1 the threshold was too low to be determined without the use of insulin or exercise to lower the blood sugar content to a point where the urine was free from dextrose.

The metabolism study made in the hospital (table 2) demonstrates the care that was exercised to protect this patient with a history suggestive of diabetes mellitus against further mismanagement. She was hospitalized for study in the nutrition laboratory. Insulin was discontinued cautiously, and determinations of the blood sugar were made at frequent intervals. This process can be followed from the brief of the metabolic study. Normal findings for blood sugar were present throughout this preliminary period. A dextrose test meal was given at this time (fig. 1, curve 2). The values for blood sugar were somewhat higher than those for normal persons, but this served only to demonstrate the effect of a lowered intake of carbohydrate preceding the test. The diet was therefore increased by 100 Gm. of carbohydrate every three days, a procedure suggested by Woodyatt [13] to aid in the diagnosis of mild diabetes. Dextrose tolerance tests were made while the patient was on diets of 200 and 300 Gm. of carbohydrate, and the results are shown in figure 1, curves 3 and 4. These tests demonstrate the normal levels for blood sugar accompanied with constant glycosuria. The patient was discharged with the diagnosis of renal glycosuria and instructed to eat a general diet. She returned at four week intervals bringing two twenty-four hour specimens of urine. Dextrose test meals were given as noted in figure 1. Many of these tests were made while the patient was pregnant, but no attempt was made to measure the effect of pregnancy on the renal threshold. The amount of sugar excreted every twenty-four hours, particularly during the last trimester of pregnancy, seemed to increase; however, no accurate determination of the intake of carbohydrate was undertaken.

The dextrose tolerance test in case 2 showed slightly higher postprandial peaks than normal. However, the findings were not diagnostic of any known metabolic disturbance. Glycosuria was present at some time during each experiment. It did not occur at the fasting level, however. The renal threshold of this subject seemed to be about 140 mg. per hundred cubic centimeters. The high value for blood sugar, 225 mg. per hundred cubic centimeters (found elsewhere), may have been caused by emotion. During the study of the patient in this laboratory a value for blood sugar of 181 mg. per hundred cubic centi-

16. Powelson, H. C., and Wilder, R. M.: Innocent Glycosuria, J. A. M. A. **96**:1562 (May 9) 1931.

meters was found during a period of momentary excitement prior to the making of the capillary puncture. This value occurred fifty minutes postprandially, shown in curve 4 (fig. 3). It was not again duplicated. Work did not seem to affect the values for blood sugar in curves 5 and 6, and this also may have been due to emotion, as the patient never became accustomed to riding the stationary bicycle used in these experiments, nor could he be reassured regarding the outcome of the tests.

Dextrose was present at some time during each of the tests made for the third patient, except when curve 4 was made, when exercise was performed. As in case 2, this glycosuria was of the cyclic type; that is, it occurred only at the levels for blood sugar found after eating and not at fasting levels. Although the postprandial values for blood sugar were rather higher than those found in many normal persons, the level did not exceed the normal renal threshold for dextrose. Yet there was marked glycosuria at these levels. The threshold for dextrose in this case, as judged from the curves for blood sugar, appeared to be approximately 150 or 160 mg. per hundred cubic centimeters.

The histories and experimental work presented in these 3 cases demonstrate that in making the diagnosis renal or normoglycemic glycosuria can easily be mistaken for diabetes mellitus. Case 1 shows this most clearly. Here a history suggestive of diabetes mellitus added to the confusion. However, the benign course of the disease over periods of from nine to fourteen years was not that of diabetes mellitus. The first patient presented symptoms of loss of weight, hunger and weakness, which might be attributed to diabetes; but physical findings were suggestive of intermittent hyperthyroidism, and these were checked by three basal metabolic rates of + 15, + 17 and + 12 per cent.

None of the 3 patients had a family history of diabetes mellitus; the third and particularly the first had excellent family histories for glycosuria. This is to be expected, for the familial characteristics appear more marked in renal glycosuria than in diabetes mellitus. Powelson and Wilder[16] reported that 23 of 91 patients with benign glycosuria showed a family history of glycosuria and said that the incidence would have been higher if the histories had been more complete. Hjärne,[2] in a study of orthoglycemic glycosuria in 199 persons interrelated by blood, described 34 cases of benign glycosuria and 7 cases of diabetes mellitus. Hjärne said he thought that marriage of persons who were probably both subjects of normoglycemic glycosuria produced no "summation" in the direction of diabetes. He concluded that the different forms of glycosuria are inheritable and are transmitted as monofactorial dominant characters but that benign glycosuria and diabetes mellitus have different origins and their occurrence in the same family is a coincidence.

The fasting level for blood sugar in all these cases was normal, with the exception of the fasting level for blood sugar taken when the first patient reported to the nutrition laboratory for the first time. At the time the blood was taken she was almost in a state of collapse and fainted momentarily. Fifteen minutes later the blood sugar was at its usual level. A normal fasting level for blood sugar is a finding on which much of the diagnosis can be based, particularly when a normal fasting level for blood sugar is accompanied with glycosuria, as in case 1. The other 2 patients, while having normal fasting levels for blood sugar, were aglycosuric at these levels.

The lack of correlation between the intake of carbohydrate and the excretion of sugar is well demonstrated by the 3 cases presented. The first patient was the only one to show to any degree an increase in the excretion of sugar with an increase in diet. This did not occur, however, in the same degree as is found in diabetes mellitus.

Respiratory quotients were not determined. The diagnosis seemed assured without these data, and, as has been pointed out by Rabinowitch [8] and Paullin,[9] patients with mild diabetes often show no changes in the respiratory quotient which would aid in differentiating them from nondiabetic persons.

SUMMARY

Three cases of normoglycemic glycosuria are reported, and a simple but adequate method of establishing such a diagnosis is presented. This method consists of frequent analyses of the sugar content of the blood by the microcolorimetric method of Folin and Svedberg and simultaneous urinalyses before and after a dextrose meal. The use of the Woodyatt forcing diet preceding the dextrose tolerance tests, as a means of excluding mild diabetes mellitus, is demonstrated.

SICKLE CELL ANEMIA IN THE WHITE RACE

IMPROVEMENT IN TWO CASES FOLLOWING SPLENECTOMY

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Sickle cell anemia until recently has been thought to be limited to the Negro race. Even in this race it is relatively uncommon, although about 7 per cent of Negroes show sickling of the red blood cells when a film of fresh blood is sealed under a cover slip for several hours (latent sickling).[1] The trait of sickling is an inborn defect[2] in the erythrocyte; so it is fundamentally a disturbance of the bone marrow, just as the characteristic spherocytosis of congenital hemolytic icterus is an anatomic defect in the formation of erythrocytes.[3] If sickle-shaped cells circulate in the blood stream, they are rapidly filtered out of the circulation by the spleen, just as are the spherocytes in congenital hemolytic icterus. The anemia characteristic of meniscocytosis is hemolytic anemia with good response of the marrow, since the bilirubin content of the blood plasma is increased and the bone marrow is overactive, as demonstrated by the hyperplasia noted at autopsy and at biopsy and by the reticulocytosis characteristic of the disease. Anemia does not develop if the sickling trait is latent, as shown by the absence of sickle cells in stained blood films and the development of sickling only in fresh preparations. The spleen early in the disease is uniformly enlarged, but later it is small and at times becomes almost completely atrophic as a result of fibrosis.

There has been no known effective treatment for sickle cell anemia. The patients do not respond to iron or liver therapy. The indication in treatment is to stop the excessive hemolysis, and in this respect the disease again resembles congenital hemolytic jaundice. If the anemia

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* Fellow in Medicine.

From the Cleveland Clinic.

1. Graham, G. S., and McCarty, S. H.: Sickle Cell (Meniscocytic) Anemia, South. M. J. **23**:598-607 (July) 1930.

2. Sydenstricker, V. P.: Sickle Cell Anemia, J. A. M. A. **83**:12-17 (July 5) 1924.

3. Haden, R. L.: The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, Am. J. M. Sc. **188**:441-449 (Oct.) 1934.

is due to rapid filtering out of the cells by the spleen, splenectomy should be valuable, just as it is in spherocytic jaundice if performed at the proper time, provided some other part of the reticulo-endothelial system does not take over the function of disposing of excessive cells after removal of the spleen. The spherocyte of congenital hemolytic icterus seems to function just as well as an oxygen carrier as the normal biconcave disk; so after splenectomy there is no excessive hemolysis, although spherocytosis persists. By analogy, the sickle cells should function equally well as normal cells and might remain for the normal span of thirty days after the filter was removed. If the cells in sickle cell anemia fragment more readily than normal, the excessive destruction of red blood cells will persist after splenectomy, since fragmented cells are disposed of by other parts of the reticulo-endothelial system after splenectomy.

In the past few years several cases of sickle cell anemia have been reported in white patients in whom there was no suspicion of Negro blood, although this possibility can never be absolutely disproved. Recently also splenectomy has been employed for a small group of patients with sickle cell anemia, without conclusive results as to its value. The two cases recited herewith are reported because they are instances of the disease in the white race and the patients have been markedly benefited by splenectomy.

Only six cases of sickle cell anemia in the white race have been reported, if the doubtful cases of Castana,[4] Archibald,[5] Stewart,[6] Lawrence[7] and Sights and Simon[8] are excluded. Cooley and Lee[9] reported the first case in 1929. Their patient, of Greek parentage, was 4 years of age and showed jaundice and enlargement of the spleen. Rosenfeld and Pincus[10] reported on a patient of Italian origin who was 9 years old. The two patients reported on by Clarke[11] were

4. Castana, V.: I gigantociti e le anemia semilunari, Pediatria **33**:431-440, 1925.

5. Archibald, R. G.: Sickle Cell Anemia in the Sudan, Tr. Roy. Soc. Trop. Med. & Hyg. **19**:389-391 (Jan.) 1926.

6. Stewart, W. B.: Sickle Cell Anemia: Report of Case with Splenectomy, Am. J. Dis. Child. **34**:72-80 (July) 1927.

7. Lawrence, J. S.: Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, J. Clin. Investigation **5**:31-49 (Dec.) 1927.

8. Sights, W. P., and Simon, S. D.: Marked Erythrocytic Sickling in White Adult, Associated with Anemia, Syphilis and Malaria: Report of Case, J. Med. **12**:177-178 (June) 1931.

9. Cooley, T. B., and Lee, P.: Sickle Cell Anemia in a Greek Family, Am. J. Dis. Child. **38**:103-106 (July) 1929.

10. Rosenfeld, S., and Pincus, J. B.: Occurrence of Sicklemia in White Race, Am. J. M. Sc. **184**:674-682 (Nov.) 1932.

11. Clarke, F.: Sickle Cell Anemia in White Race with Report of Two Cases, Nebraska M. J. **18**:376-379 (Oct.) 1933.

brothers, aged 11 and 3, born of Sicilian parents. Cooke and Mack[12] reported on siblings, aged 1 year and 3½ years, of white American-born parents. In each instance a careful investigation was made to exclude Negro ancestry, though this cannot be absolute.

Splenectomy as a therapeutic measure in sickle cell anemia has been performed in few instances since first suggested by Sydenstricker.[13] The literature on splenectomy has been well reviewed by Ching and Diggs,[14] who reported an attempted splenectomy in an 18 year old Negress. In this instance the spleen was so small it could not be found, and the patient died soon after the exploratory operation. Only ten cases have been reported in which splenectomy has been performed.[15] All the splenectomies have been performed on young children, and in most instances the spleen has not been excessively large. The weights recorded have been 186 and 194,[15c] 621,[15e] 655,[15i] 112,[12] 200[15f] and 295 Gm.,[15g] respectively. In Stewart's case[6] the spleen had been large but was small at the time of operation. In Hahn's cases,[15a,d] the size of the spleen was recorded as three and four times, respectively, the normal adult size. It is interesting to note that the greatest improvement has followed the removal of large spleens. In none of the cases, when reported, had the patient originally been followed long enough to determine the ultimate value of splenectomy. Landon and Patterson,[15i] in reporting a case recently, summarized the end-results in cases

12. Cooke, J. V., and Mack, J. K.: Sickle-Cell Anemia in White American Family, J. Pediat. **5**:601-607 (Nov.) 1934.

13. Sydenstricker, V. P.: Sickle Cell Anemia, South. M. J. **17**:177-183 (March) 1924.

14. Ching, R. E., and Diggs, L. W.: Splenectomy in Sickle-Cell Anemia: Report of Case with Necropsy in Adult on Whom Splenectomy Was Attempted, Arch. Int. Med. **51**:100-111 (Jan.) 1933.

15. (*a*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of Case Greatly Improved by Splenectomy; Experimental Study of Sickle Cell Formation, Arch. Int. Med. **39**:233-254 (Feb.) 1927. (*b*) Stewart.[6] (*c*) Bell, A. J., and others: Sickle Cell Anemia: Reports of Two Cases in Young Children in Which Splenectomy Was Performed, Am. J. Dis. Child. **34**:923-933 (Dec.) 1927. (*d*) Hahn, E. V.: Sickle Cell (Drepanocytic) Anemia with Report of Second Case Successfully Treated by Splenectomy and Further Observations on Mechanism of Sickle-Cell Formation, Am. J. M. Sc. **175**:206-217 (Feb.) 1928. (*e*) Landon, J. F., and Lyman, A. V.: Sickle-Cell Anemia with Case Report of Splenectomy, ibid. **178**:223-228 (Aug.) 1929. (*f*) Leivy, F. E., and Schnabel, T. G.: Abdominal Crises in Sickle-Cell Anemia, ibid. **183**:381-391 (March) 1932. (*g*) Bothe, F. A.: Splenectomy for Sickle-Cell Anemia, Ann. Surg. **97**:146-150 (Jan.) 1933. (*h*) Cooke and Mack.[12] (*i*) Landon, J. F., and Patterson, H. A.: Evaluation of Splenectomy in Treatment of Sickle-Cell Anemia: Late Results of Two Cases So Treated with Summary of Present Condition of All Reported Splenectomized Patients, J. Pediat. **7**:472-477 (Oct.) 1935.

reported sufficiently long before for a follow-up to be of value. All the patients were living. In Mitchell's case [15c] splenectomy, performed six years previously, did "no particular good." In all other cases [16] the patients were clinically well, although still anemic. Bothe's patient [15g] had been splenectomized two years before the report was made and was greatly improved. Our two patients have been followed for fourteen and five years, respectively, since operation. In each instance the splenectomy was performed with an incorrect diagnosis of Banti's disease, because of the obscure anemia and splenomegaly. The correct diagnosis was made in a check-up of splenectomized patients when sickle cells were noted in stained blood films and marked sickling was demonstrated in fresh preparations. Further study of the sections of the spleens removed shows many sickle cells in the capillaries.

The parents of the two sisters reported on in this paper were born in Sicily. One patient was born in Sicily, the other in this country. Close questioning elicited no family features suggesting the presence of Negro blood. The parents' families had been associated for generations in Sicily, where there were no Negroes. The father of our two patients died of a blood dyscrasia for which a diagnosis of myeloid leukemia was made, although some unusual features were presented. He had jaundice, an enlarged spleen, marked anemia and leukocytosis, with the development of many myelocytes in the blood after his admission to the hospital. With roentgen therapy the white cell count decreased, but the anemia was progressive, and death occurred when the patient was at home three months after admission to the hospital. The seven children were studied at that time, and our second patient was found to have a large spleen. Unfortunately, the possibility of sickle cell anemia was not considered in the father's case; so no special studies were made. The mother's blood was normal, and the father had a congenital flexion deformity of both little fingers, similar to that in our first patient. Leukocytosis is fairly constant, and myelocytosis is frequent in sickle cell anemia; so it seems possible that the father died of an acute exacerbation of sickle cell anemia with a marked bone marrow reaction. Three other children in the family were examined recently, but no significant physical findings were noted. The blood of one brother showed sickling in fresh preparations, although he had no significant anemia. The history of the flexion deformity of the little finger in the family history is interesting. The occurrence of this anatomic defect in the father of our patients has already been mentioned. A similar deformity was present in the paternal grandfather, a brother, an aunt and two cousins of our patients.

16. Stewart.[6] Hahn and Gillespie.[15a] Bell and others.[15c] Hahn.[15d] Landon and Lyman.[15e]

REPORT OF CASES

CASE 1.—A. B., now aged 21 years, was first seen when 8 years of age because of loss of appetite, recurrent sore throat, fever, weakness, pallor and jaundice. These symptoms began at the age of 5 years and occurred in attacks lasting one to two weeks. At the original examination she appeared poorly nourished, the scleras were icteric, the spleen extended down to the iliac crest and the tonsils were infected. She then had mild anemia (4,000,000 red blood cells and 70 per cent hemoglobin) and a white cell count of 22,000. The Wassermann reaction was negative. The spleen was removed by Dr. G. W. Crile on Oct. 31, 1922. For ten years the patient remained free from symptoms and then was readmitted to the hospital. A diagnosis of rheumatic heart disease with mitral stenosis was made. Physical examination showed mitral stenosis and inefficiency, with a competent heart, and no other significant findings. She has the flexion deformity of the

Fig. 1.—Photograph of the hands of A. B., showing the flexion deformity of the little finger.

little finger previously mentioned (fig. 1). The findings in the blood are detailed in the accompanying table. Sickle-shaped and oat-shaped cells are always found in stained preparations (fig. 2*A*), and fresh preparations on standing show sickling of all cells (fig. 2*B*). Blood counts have been made frequently over a period of four years. The number of erythrocytes is usually normal, with a decreased hemoglobin content and color index. There are usually leukocytosis, reticulocytosis and an increase in the bilirubin content of the plasma. A period of intensive intramuscular liver therapy and the administration of 60 grains (3.6 Gm.) of pills of ferrous carbonate daily caused no change in the blood picture. She has continued to have pains in the joints that are more characteristic of those in sickle cell anemia than in rheumatic fever, but otherwise she is clinically well.

CASE 2.—F. B., a sister of A. B., was admitted to a hospital at the age of 15 because of increasing splenic enlargement and pallor. She had been told that she had a large spleen when 11 years of age. She had become increasingly weak

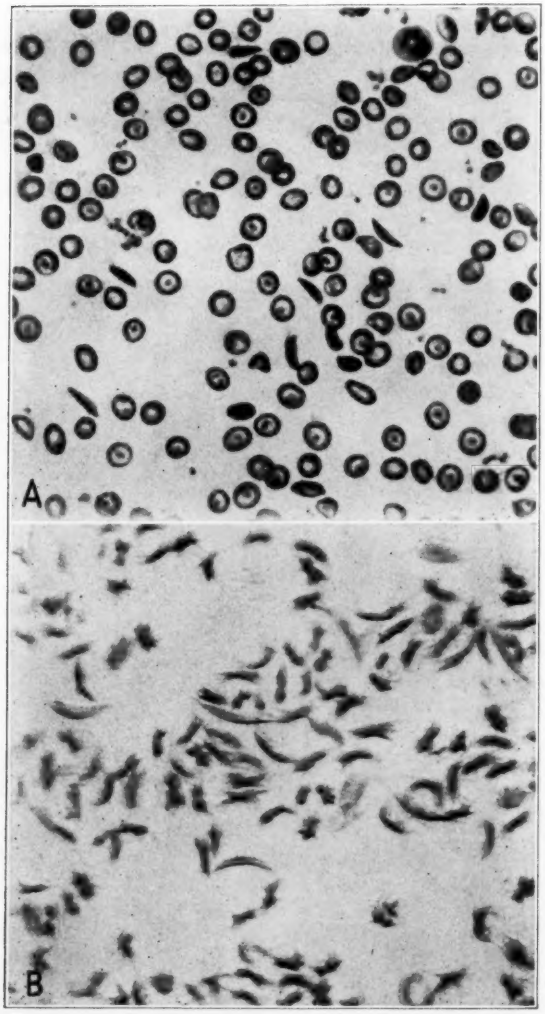

Fig. 2.—*A*, photomicrograph of a stained blood film in case 1 (A. B.). This picture shows sickle cells and the dimpling of the central area of many red blood cells. *B*, photomicrograph of a fresh preparation of blood in case 1, showing sickling of red blood cells.

and icteric. On examination there were no significant physical findings, except enlargement of the spleen, which extended down to the iliac crest and nearly to the midline. The edge of the liver was palpable 2 fingerbreadths below the costal margin in the nipple line. The blood count showed 3,690,000 red blood cells, 60 per cent hemoglobin and 6,650 white blood cells. The differential count was not abnormal, and the icterus index was 11. The clinical diagnosis was Banti's disease. The spleen was removed by Dr. Claude S. Beck on July 27, 1931. After the splenectomy there was a stormy course. The anemia became much more marked, and the white cell count rose to 60,000, with myelocytes and many nucleated red blood cells. This postoperative reaction was similar to the blood picture presented by the father without treatment.

The patient has considered herself in good health since the operation, and physical examination now reveals nothing significant. The findings in the blood are given in the accompanying table. The fresh preparations show marked sickling.

Pathologic Study of the Removed Spleens.—Case 1: The spleen weighed 480 Gm., had a smooth capsule, was firm and on section cut with considerable resist-

Data on the Blood

Case 1	Red Blood Cells, per Cu. Mm.	Volume of Packed Erythrocytes (% of Normal)	Volume Index	Hemoglobin, Percentage	Color Index	Saturation Index	White Blood Cells, per Cu. Mm.	Icterus Index	Reticulocytes, Percentage
9/14/32	4,390,000	71	0.81	71	0.81	1.00	9,900	8	...
11/23/33	4,580,000	75	0.81	65	0.71	0.87	8,900	10	...
2/19/34	4,670,000	75	0.81	65	0.70	0.87	11,150	20	...
3/31/34	4,630,000	73	0.78	65	0.70	0.89	10,750	15	...
2/28/35	4,850,000	73	0.75	65	0.67	0.89	15,100	15	...
3/27/35	4,470,000	69	0.77	58	0.65	0.84	10,650	15	7.0
5/ 8/35	4,600,000	75	0.82	61	0.66	0.81	15,550	10	...
Case 2									
2/18/34	4,360,000	77	0.88	65	0.75	0.84	8,600	15	3.2
5/11/35	4,350,000	73	0.84	61	0.70	0.84	8,800	8	...
8/31/35	4,140,000	69	0.83	58	0.70	0.84	12,750	10	...

ance, suggesting diffuse fibrosis. On histologic study it showed thickening of the trabeculae and engorgement and hemorrhages in the pulp. Altered blood pigment was seen in numerous wandering cells and polymorphonuclear leukocytes. Material stained bluish black and giving the characteristic reaction for iron with special stains was observed in cells, in masses and in threads associated with trabeculae. In many places most of the material contained in foreign bodies took the stain for iron. The striking feature in the stained reactions was the appearance of chronic diffuse inflammation, with circumscribed areas of degeneration of elastic tissue or trabeculae and deposition of iron pigment.

The diagnosis was chronic diffuse splenitis with considerable deposition of iron pigment.

The sections have been examined again in the light of recent studies of the blood, and many sickle cells have been observed.

Case 2: The spleen weighed 700 Gm. The capsule was smooth but slightly thickened. The spleen showed increased resistance on section. Histologic sections showed the trabeculae slightly increased in thickness, with partial hyalinization. The connective tissue was definitely increased. The cellular pulp tissue was decreased, and a large quantity of blood was present. A section of liver removed at operation showed nothing unusual.

The diagnosis was splenomegaly, with a definite increase in the connective tissue reticulum. A note was made that the histologic appearance was consistent with the clinical diagnosis of Banti's disease.

A recent review of these sections showed marked sickling of the red blood cells in vessels and sinuses.

COMMENT

These two cases seem undoubted instances of the occurrence of sickle cell anemia in the white race. Here, as in the other six cases reported, however, the occurrence of Negro blood cannot be excluded absolutely. It is possible that at some time an admixture occurred, although there is nothing in the history or physical findings to suggest this. The familial occurrence of the flexion deformity of the finger in this family is of great interest, since sickle cell anemia is considered a similar anatomic defect in the shape of the erythrocyte. There seems little doubt that the bone marrow is primarily at fault in this disease and forms red blood cells that are abnormal in shape and perhaps in quality.

It is most difficult to evaluate the efficacy of splenectomy here. Both patients had well marked anemia and symptoms dependent on the anemia prior to operation. Since operation both patients have considered themselves well so far as symptoms referable to the anemia are concerned. The study of the blood of both, however, shows that they have anemia which is not marked enough to produce symptoms. The clinical course of sickle cell anemia is highly variable; it may continue to be mild, or it may run a progressively downhill course. As a rule, patients who are not operated on become steadily worse. There is no way of knowing what course the disease would have taken in our cases if the spleen had not been removed. The patients think they have been much helped by operation, and it is our opinion that they have been. They continue to have excessive hemolysis, however, indicated by the increased icterus index, showing that accelerated filtration of cells by the spleen is not the sole cause of the anemia.

The removal of the spleen, if it is large, is a logical procedure in sickle cell anemia. The disease is a hemolytic disorder, and the spleen early, at least, is one seat of excessive destruction of red blood corpuscles. Hemolysis continues after the spleen becomes small, and the anemia of the disease has not been cured in any patient with splenectomy, although it has become definitely less severe. It is apparent that hemolysis here must be continued by some tissue other than the spleen, probably some other part of the reticulo-endothelial system. The first stage in the normal disposal of red blood cells after the usual span of life in the circulation is fragmentation. The evidence indicates that in sickle cell anemia the red blood cells become fragmented more readily than normal, so there must be two factors in the excessive

hemolysis characteristic of the disease. These are excessive removal of red blood cells from the circulation by the spleen, because of the abnormal shape, and excessive fragmentation in which the spleen has no primary part. It is apparent that there is no indication for removal of the spleen unless it is large. The spleen is probably always large early in the disease. Since there is no other satisfactory treatment of the disease, splenectomy should certainly be tried; if the spleen is large, operation should be undertaken, however, with the realization that it affects only one factor in the excessive hemolysis. There is every indication that removal of a small spleen late in the disease is a great

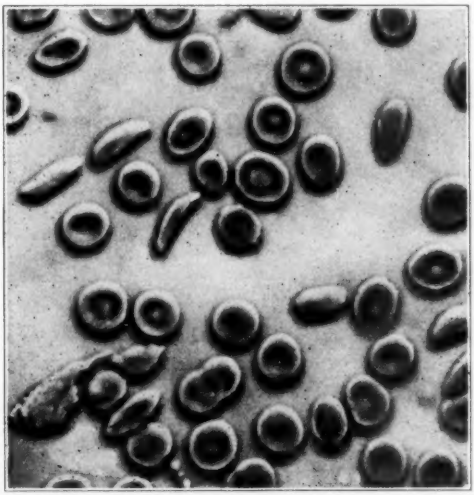

Fig. 3.—Bas-relief photomicrograph showing the shape of the dimpled red blood cells in sickle cell anemia.

operative risk and is not justifiable. At this stage it cannot have much to do with the excessive destruction of cells.

The two cases reported emphasize again the necessity for considering sickle cell anemia as a clinical possibility in obscure cases of anemia, even in the white race. More cases will certainly be found if searched for.

The slides of the blood of our two patients show clearly a characteristic of the red blood cells in sickle cell anemia which we have not seen referred to in any discussion of the disease. Many of the cells which are not sickled, instead of being biconcave disks, have a central, sugar-loaf elevation, so that a cross-section has the appearance of a Mexican hat instead of the normal dumb-bell. Almost all the illustra-

tions of the blood previously published show this peculiar shape. It is depicted especially well in the illustration of the blood of the patient reported on by Landon and Lyman.[15e] This effect can be shown best in bas-relief photomicrographs (fig. 3). This unusual shape must be related in some way to the abnormal tendency to hemolysis in sickle cell anemia and may determine the ease of fragmentation. One occasionally sees a few cells of this shape in other anemias, but they are never present in any significant number except in sickle cell anemia. They were constant in all the cases in which we have made an examination.

In our two cases a number of special measurements of the red blood cells were made without finding anything significant. The cell thickness as determined from the mean diameter and volume was normal. The mean diameter was slightly decreased, as was the volume. The volume-thickness index, which indicates the relation of the diameter to the thickness, was normal.

One patient had a thorough trial with liver extract administered intramuscularly and at another time with large doses of iron, neither of which influenced the anemia; so there is evidently no deficiency in specific building material in this disease. The blood of both patients showed beginning hemolysis in a 0.42 per cent solution of sodium chloride, and the hemolysis was not complete in a 0.28 per cent solution; so the fragility was slightly decreased.

SUMMARY AND CONCLUSIONS

Two white patients with sickle cell anemia are reported on.

The patients are sisters, born of Sicilian parents.

There is no history or physical finding suggesting an admixture of Negro blood.

Both patients have had the spleen removed, with marked benefit.

In one case the spleen was removed fourteen years ago and in the other five years ago.

Both patients continue to have mild hemolytic anemia but are clinically well.

In sickle cell anemia there seem to be two factors in the excessive hemolysis characteristic of the disease, viz., excessive filtration of abnormally shaped cells and excessive fragmentation or early death of the cells.

The results obtained in these cases suggest that splenectomy should be employed more often in sickle cell anemia if the spleen is large and the patient is seen early in the disease. It is not a cure but only an aid in treatment, since anemia persists.

CLINICAL SYMPTOMS OF CHRONIC GASTRITIS

OBSERVATIONS ON THIRTY-FIVE SELECTED CASES

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Since the demonstration by gastroscopy of the frequent occurrence of chronic gastritis,[1] gastroscopists have often stated that this disease does not show a definite symptom complex.[2] Advanced gastric cancer and chronic round ulcer of the stomach may exist with mild or no subjective complaints, yet it is rare for chronic disease to exist anywhere in the body without being accompanied with some symptoms which aid the physician in his diagnostic attack on the organ involved. In the cases of mildest cystitis some tenesmus or urinary frequency points to possible disease of the bladder, just as diarrhea points to possible disease of the bowel. It would be a rare anomaly if the stomach remained free from all symptoms referable to it in advanced chronic inflammation of its walls.

With the idea of emphasizing a syndrome or at least of indicating symptoms most frequently present in chronic gastritis, we selected for this report from among three hundred and forty-nine patients with chronic gastritis diagnosed by means of the gastroscope at the Billings Hospital, twelve with the superficial and twenty-three with the hypertrophic variety. The atrophic variety was not included because an insufficient number of patients were left after elimination according to our rather rigid requirements. We included no patients who presented a gastroscopic picture of chronic gastritis in whom a demonstrated func-

1. Schindler, R.: Die diagnostische Bedeutung der Gastroskopie, München. med. Wchnschr. **69**:535, 1922; Lehrbuch und Atlas der Gastroskopie, Munich, J. F. Lehmann's Verlag, 1923.

2. Hohlweg, H.: Beobachtungen und Betrachtungen auf Grund von 100 Gastroskopien, München. med. Wchnschr. **71**:506, 1924. Gutzeit, K.: Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Ergebn. d. inn. Med. u. Kinderh. **35**:1, 1929. Henning, N.: Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934. Moutier, F.: Traité de gastroscopie, Paris, Masson & Cie, 1935. Schindler, R., and Ortmayer, M.: Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method, Arch. Int. Med. **57**:959 (May) 1936.

tional or organic disorder might account for the symptoms in the digestive tract. This excluded patients with a positive Wassermann reaction, arteriosclerosis, demonstrable gastric or duodenal ulcer, cirrhosis of the liver, cardiac disease, pernicious anemia, marked psychoneurosis, colitis of any variety, disease of the gallbladder, diabetes, carcinoma of the abdominal organs, hypertensive cardiovascular renal disease, migraine and menopausal symptoms and patients in whom combinations of two types of gastritis were found by gastroscopic examination—in short, all patients for whom some other tenable diagnosis could be made, even when we did not always agree that the symptoms should be accounted for on the basis of the other diseases. We wish to emphasize that in the patients eliminated because of the presence of other diseases there was undeniable evidence of chronic gastritis also. Future research will be needed to determine whether the gastric disorder or the other disease was responsible for the abdominal symptoms.

The following tabulation briefly indicates the number of cases and the sex distribution of the two types of chronic gastritis:

Chronic Gastritis

	Males	Females	Total
Hypertrophic variety	22	1	23
Superficial variety	5	7	12
	27	8	35

Although a few patients were under 30 years of age and a few were over 50, none were younger than 20 or older than 59 years, and twenty-five were in the fourth or fifth decade.

The duration of illness was on the whole prolonged. Only one of the patients (with hypertrophic gastritis) dated the onset of illness a month previously. Twenty-six patients had had symptoms for from two to twenty years, while nine had had symptoms for from one to eighteen months. Patients with hypertrophic gastritis had had an average duration of symptoms of four years. Those with superficial gastritis had had an average duration of symptoms of three and three-fifths years.

Of the twenty-five patients who made definite mention as to periodicity or constancy of the symptoms, four with superficial gastritis had periodic and five had constant (daily) distress. Of those with hypertrophic gastritis thirteen had periodic and three had constant distress.

The symptom most common to all these patients was the location of the distress. Thirty-two of the patients complained of localized distress, twenty-seven referring it to the epigastrium and five to the upper half of the abdomen (two referred it to the right upper quadrant, one to the substernal region and two to the left and right upper quadrants). Two of the remaining three patients stated that their distress

was "general." Radiation occurred rarely (four times) to the lower portion of the abdomen, to the nipples or to the back.

The type of distress varied as greatly as it does with ulcer or cancer of the stomach. Dull pain, burning, gnawing, vague distress and a feeling of fulness, distention or pressure seem to be common symptoms in chronic superficial and hypertrophic gastritis, just as are belching and sour eructations. Nausea was mentioned by only four of the patients with hypertrophic gastritis and vomiting by four with hypertrophic and three with superficial gastritis. Hematemesis was mentioned by only one patient of the group; he had superficial gastritis, but it is well known that gross gastric hemorrhage may occur in all types of gastritis. Severe pain was mentioned by none of the patients with superficial gastritis and by six with hypertrophic gastritis. Heartburn, sour regurgitation, "gas," griping, crawling, bloating and borborygmi were occasionally mentioned. Loss of appetite and increase of appetite were rare symptoms in this group, contrasting with statements of gastroscopists based on larger, less rigidly selected material.

The distress in relation to the taking of food in patients with superficial gastritis occurred within the first half-hour in five cases and within from one to four hours in six cases. Midnight distress was mentioned by one. In contrast to the patients with superficial gastritis, none of the patients who had hypertrophic gastritis complained of distress immediately or within thirty minutes following a meal. Seventeen complained of the onset from one to four hours after meals. Two had midnight distress. Two were indefinite, saying their distress occurred "after" meals. One mentioned "no relationship" to eating.

Aggravation of distress was caused most frequently either by unrestricted or large amounts of food or by certain foods, this factor being mentioned by ten of the thirty-five patients.

Relief from distress was obtained by eating far less constantly by these patients than in our experience with patients suffering from chronic uncomplicated benign round gastric or duodenal ulcer. Nine (39 per cent) with hypertrophic and four (33.3 per cent) with superficial gastritis, however, had complete and definite relief after eating.

Relief from pain by alkali was obtained by eleven (47.8 per cent) of the patients with hypertrophic gastritis and by eight (66.6 per cent) with superficial gastritis, a total of nineteen (54.2 per cent) of the thirty-five patients. Vomiting, belching, aspiration and bland diets gave relief in a small proportion of cases.

Since all patients with disease that might contribute to the production of abdominal symptoms were eliminated from this review, it is not strange that practically all who were included were free from abnormal physical findings or symptoms referable to other systems. Ten men-

tioned "nervousness" of an indefinite sort, a few had headaches and six spoke of a marked loss of weight. They were singularly free from disturbance of bowel function and excessive use of cathartics. Eighteen of the patients had one or two normal bowel movements daily. Six had hard stools, and six had mushy or watery stools. The remainder were not specific as to the frequency or nature of the stools. Six of the patients used cathartics oftener than once a week. The only physical finding noted, and that occasionally, was abdominal tenderness (five of the patients with hypertrophic gastritis noted tenderness in the epigastrium, one to the left of the umbilicus, three in the right upper quadrant, four in the left lower quadrant and two in the right lower quadrant; while one of the patients with superficial gastritis noted distress in the upper portion of the abdomen, and one noted it in all four quadrants). It is possible that if mild degrees of tenderness had been carefully searched for they might have been found more often—for instance, the zone of tenderness to the left of and below the umbilicus.[3] But it will be noted that many of these patients were examined in departments other than that of gastro-enterology, and in our opinion this gives a better cross-section of signs and symptoms than the more minute investigation of the trained specialist, especially when the histories and results of examinations agree when checked by the cooperating department.

Laboratory procedures for these patients showed negative Wassermann and Kahn reactions and normal urine and blood. Gastric analyses were made for thirty-two of the thirty-five patients. Twenty-two of the patients with hypertrophic gastritis (one not tested) showed free hydrochloric acid by the Ewald or histamine test. Of those with superficial gastritis, nine showed free hydrochloric acid, and one showed no free hydrochloric acid (Ewald test meal); two were not tested. For the thirty-one patients who showed free hydrochloric acid in test meals, the range of free hydrochloric acid was from 11 to 100 points. A negative result for the benzidine test of the stools of thirty patients and a one plus reaction for five patients were recorded.

Roentgenograms of the esophagus, stomach and duodenum of thirty-two of these patients were normal. In one a diagnosis of spastic hourglass stomach was made; in another, thickening of the gastric rugous folds, and in a third, "marked gastritis" (type not mentioned). In nineteen instances the colon was studied roentgenographically and was normal, and in five instances the gallbladder was observed to be normal. It is obvious that lesions of the colon and gallbladder were infrequently suspected, because of the relative infrequency of roentgenographic studies in this series.

3. Schindler, R.: Die klinische Diagnose der Gastritis chronica, München. med. Wchnschr. **73**:482, 1926.

The gastroscopic findings will be reviewed in greater detail, as they represent the positive diagnostic signs for these patients. Of the twelve patients with superficial gastritis, the entire stomach, including the pylorus, was visualized in nine, part of the antrum gastroscopically and the body in two and the region above the angulus in one. In two patients the entire gastric mucous membrane was observed to be involved in gastritic changes, in six there were changes noted above the angulus, and in four there were seen localized or circumscribed areas of gastritis. The degree of gastritis was described as marked in seven and slight in five. Changes in the mucous membrane or in the secretion or both were noted in all patients. Hemorrhage or erosion of the mucous membrane or both were seen in six. Neither the degree of gastritis, i. e., its severity, nor the presence of hemorrhage or erosion was associated with severity or aggravation of distress in these patients.

Of the twenty-three patients with chronic hypertrophic gastritis, the entire stomach with the pylorus was visualized in eighteen, the body and part of the antrum in three and the stomach above the angulus in two. In two patients the entire gastric mucosa was involved in hypertrophic changes, in two only the antrum, in twelve the stomach above the angulus and in the remaining seven some localized or circumscribed area of the stomach. Changes in the mucous membrane typical of hypertrophic gastritis were noted in all of these patients. Abnormal secretion was mentioned for only one. Hemorrhage or erosions of the mucous membrane were seen in seven. Again, severity of the gastritis, of the erosions or of the hemorrhage apparently was not associated with an aggravation of symptoms.

In order to illustrate the typical clinical history and picture, we cite in detail the following reports:

Case 1.—D. H., a man aged 35, had symptoms from the time a horse kicked him in the abdomen. The distress, however, did not begin until some time later. For ten years, from spring to winter, while ploughing and engaged in considerable physical exertion, the patient experienced dull midepigastric pain which came on two hours after meals and lasted for from one to three hours. At times it was so severe in the afternoon that he had to stop work. The pain was relieved by food, milk and fasting. The attending physician regarded this history as "classic for ulcer." Soda, however, aggravated rather than relieved the distress. Ulcer management aggravated it. Pain continued on management of the bowels. An appendectomy four years earlier had not relieved it. The patient was a worrier. He had no other symptoms or past history worthy of note. He had normal stools once daily without catharsis.

Physical examination revealed only epigastric tenderness.

The Ewald test showed free hydrochloric acid of 63 and total acid of 82. The stools were normal. A motor meal showed that there was no retention. The urine and blood were normal. Roentgenograms showed that the esophagus, stomach, duodenum and chest were normal.

Gastroscopic Examination.—At first the pylorus was seen, without peristalsis, as a small opening with a reddish edge. The redness was succeeded by gray mucous membrane, which turned to the normal orange. Then vigorous peristalsis began. The antrum was perfectly normal. On the posterior wall the mucous membrane was intensely swollen and contained numerous hemorrhagic stripes and flecks and larger gray and reddish spots. Above this point the mucous membrane of the corpus was normal. In the fornix, especially on the anterior wall, there was seen an extensively thickened and dimpled mucous membrane, with small pits and crevasses.

Diagnosis.—The gastroscopic diagnosis was chronic hypertrophic hemorrhagic gastritis of a circumscribed area on the lower posterior wall of the corpus and the anterior wall of the fornix.

The clinical diagnosis, before gastroscopy, was peptic ulcer (?); after gastroscopy it was chronic hypertrophic hemorrhagic gastritis.

CASE 2.—W. F., aged 32, an electrical engineer, who worked hard and under high tension, seemed to precipitate distress by short periods of excessive use of alcoholic liquors. For six years he had had periodic attacks of severe gnawing to knifelike pain localized to an area the size of the hand in the epigastrium and radiating through to the back at the same level. Usually he had one such period a year, lasting three or four weeks or longer. The pain appeared one or one and a half hours after meals, often three times a day, and was relieved regularly and usually completely by alkali, food and emptying the stomach. Milk taken in the midmorning or afternoon often warded off the distress. Rarely was distress present at night. While under observation but not on treatment, the patient had some severe pain at night.

The remainder of the history showed no relationship to the digestive distress, except for an attack of jaundice of several months' duration when he was 10.

Physical examination revealed only slight tenderness and resistance in the epigastrium.

An Ewald test showed free hydrochloric acid of 70 and total acid of 82. Six benzidine tests of the feces showed a negative reaction, one showed a 3 plus reaction and one showed a 1 plus reaction.

Examinations of the urine and blood revealed no abnormality.

Roentgenographic examination in 1933, after the oral administration of dye, gave faint visualization of the gallbladder. The esophagus, stomach and duodenum were normal. On April 12, 1934, there was normal visualization of the gallbladder (oral dye). The esophagus, stomach and duodenal bulb were normal. On April 18 there was no roentgenographic evidence of a duodenal ulcer.

Gastroscopic Examination.—On April 27, 1935, the mucous membrane of the upper part of the stomach was normal, but that of the lower part was markedly swollen and velvet-like.

Diagnosis.—The gastroscopic diagnosis was chronic hypertrophic gastritis of the lower part of the stomach. The clinical diagnosis (made after gastroscopy was performed) was suspected gastric or duodenal ulcer. Our diagnosis was chronic hypertrophic gastritis.

CASE 3.—E. C. H., a man aged 33, complained of burning and at times recurring sharp pain in the left upper quadrant of the abdomen for two years, recurring every two to four days and present for the same length of time. He mentioned one interval of five weeks of freedom from pain. His distress came on two or three hours after meals, lasting longer after the noon and night meals than after breakfast, from one-half to two hours, as a rule. A bismuth preparation which he

had been taking for several months, though not until lately during distress, gave him relief from pain in thirty minutes. Two grams of sodium bicarbonate afforded relief from pain within fifteen minutes, as a rule. A full meal usually relieved his distress for two or three hours. The patient thought his distress became worse when he assumed a "fuller" diet. He complained also of occasional dull pains around "the appendix" and of loss of appetite. There was constipation when he was in most distress, and for this he would resort to daily enemas, which neither relieved nor brought on distress. The history otherwise was unimportant.

An Ewald test showed free hydrochloric acid of 27 and total acid of 50. Three benzidine tests of the stools gave negative reactions. Examinations of the blood and urine revealed no abnormality.

Roentgenographic examination showed that the esophagus, stomach, duodenum and colon were normal.

Gastroscopic Examination.—The entire stomach, with the exception of the lesser curvature of the antrum, was seen. The antrum was normal. In the greater curvature and in the posterior wall, at the height of the angulus, there were definite changes. The mucous membrane contained large hemorrhages, in which one marked erosion was seen. Grayish spots were noted in the higher parts of the anterior wall.

Diagnosis.—The gastroscopic diagnosis was superficial hemorrhagic, erosive gastritis. The clinical diagnosis was the same.

CASE 4.—L. M., a woman aged 41, first seen in the clinic on June 17, 1935, was hospitalized on July 5. She complained of periodic distress, localized in the epigastrium, which had been present for years and until the past two weeks had been relieved by taking food and sodium bicarbonate. Previous periods of distress had lasted about two weeks and had recurred at three or four month intervals. The distress for which she came to the clinic was the severest she had had. It came on one or two hours after meals. Food and soda were giving considerable but not complete relief in this attack. The pain was radiating directly through to the back and had awakened her several times at night. At night the pain was relieved by eating. It might occur at 2 a. m., waking her, and recur at 4 and at 6 a. m. No nausea, vomiting or loss of weight was noted. She had a good appetite. Bowel movements were regular without catharsis. There were no other symptoms of significance.

Physical examination revealed only exquisite epigastric tenderness. The temperature and pulse rate were normal.

The Ewald test showed free hydrochloric acid of 47 and total acid of 68. One benzidine test of the feces showed a negative reaction. Three other tests showed a reaction of from 1 to 3 plus. Examinations of the blood and urine revealed no abnormality. The urea clearance test showed a value of 72 per cent. Scratch tests showed a questionably positive reaction for milk products and white of egg.

Roentgenographic examination on June 19 showed that the stomach and duodenum were normal, and on July 8 the stomach, esophagus, duodenum, gallbladder and colon were shown to be normal.

Gastroscopic Examination.—On July 11 the entire stomach, except the lesser curvature of the antrum, was well seen. There was no change in the antrum. The crests of the folds of the lesser curvature, the anterior wall and the body showed marked changes. There were many small red spots and streaks. In the valleys between the folds there were no changes.

Diagnosis.—The gastroscopic diagnosis was marked superficial gastritis. The clinical diagnosis was not definitely made. Our diagnosis was chronic superficial gastritis.

The following case report is interesting because of coexistent erosive hypertrophic gastritis and chronic ulcerative colitis. This patient was not included in the group reported on in this paper, because of the complicating ulcerative colitis; hence this report will serve to illustrate the type of case discarded, as well as a combination of gastric and intestinal disorders, the former being entirely forgotten by the attending physician in making the final diagnosis.

CASE 5.—E. R., a man aged 32, six months earlier and again for four weeks preceding his first visit to the clinic, experienced epigastric distress coming on regularly from two to four hours after meals, in the midmorning, midafternoon and late evening, and slightly before breakfast. This distress was relieved regularly by food, which he had learned to take even on retiring. A bland diet prevented occurrence of distress. The only significant event in the past history was a short attack of cramps and diarrhea, without the presence of blood being noted in the stools, one year earlier.

Physical examination on Sept. 25, 1934, revealed no abnormality except mild epigastric tenderness.

The Ewald test showed free hydrochloric acid of 43 and total acid of 58—normal values. The benzidine test of the feces showed a negative reaction. The urine and blood were normal.

Roentgenograms showed that the esophagus, stomach and duodenum were normal.

On October 12 the patient returned to the clinic with a new complaint. The epigastric distress had been improved by a bland diet, but mild to severe abdominal cramps had developed on October 10, with three or four loose stools each day. Physical examination added nothing new. Examination of the stools on October 12, 15, 16 and 17 did not reveal Endamoeba histolytica.

Gastroscopic Examination.—A thick, edematous mucous membrane was seen, with small creases and one small erosion on the anterior wall. Other portions of the stomach were normal.

Further Data.—Proctoscopy, on October 26, showed scattered superficial ulcerations with undermined edges, which suggested those of amebic dysentery. After October 26 the stools showed pus and blood (2 plus). No amebas, cysts or ova were found.

On October 31 the patient was hospitalized because of chills and fever and persistence of diarrhea, and a rather stormy course of illness followed. Fever with exacerbations and chill, leukocytosis, diarrhea, anemia requiring transfusions, finally redness of the ankle joints, pain, tenderness and a loss of 22 pounds (10 Kg.) in weight were the chief symptoms. These slowly receded after several months, when he was discharged to rest in bed at home. The stools showed no E. histolytica or Bacillus dysenteriae throughout the patient's stay in the hospital. The feces showed profuse amounts of pus and blood. On November 5 a heavy growth of green streptococci was obtained. Culture of the blood was sterile. There was no agglutination for typhoid or paratyphoid A and B serum. The urine was normal throughout.

In April 1935 the patient's wife wrote that he had gained 40 pounds (18 Kg.).

Diagnosis.—The gastroscopic diagnosis, made on Oct. 13, 1934, was chronic erosive hypertrophic gastritis. The clinical diagnosis, made on October 31, was chronic ulcerative nonspecific colitis and arthritis; this clinical diagnosis was repeated when the patient was discharged, on Jan. 27, 1935.

COMMENT

We selected twelve patients with chronic superficial gastritis and twenty-three with chronic hypertrophic gastritis from among three hundred and forty-nine patients with superficial, hypertrophic and atrophic gastritis, so diagnosed by means of the gastroscope, in order to analyze the clinical pictures in detail. Many more patients might have been included in whom gastritis was found in combination with other disease entities and who referred their symptoms to the gastro-intestinal tract. It is obvious that these symptoms might have been due to the gastritis, but it could be argued that they occurred because of the other diseases present. An insufficient number of patients with "pure" atrophic gastritis—uncomplicated by other disease—were on hand to include an analysis of this form of gastritis.

Observations on patients with a combination of superficial and atrophic gastritis were omitted. This combination has frequently been seen, and in our opinion the atrophic variety is a sequela of the superficial variety.

By analyzing even a few cases of two of the forms of chronic gastritis in their purest and most uncomplicated state, we believe that we are presenting a clinical picture valuable in the differential diagnosis of gastric disease. However, we wish to emphasize that this picture is necessarily incomplete.

Among patients with superficial gastritis, about 50 per cent show periodic distress and 30 per cent constant distress. The distress is located in the upper portion of the abdomen, chiefly epigastric, and is characterized by burning, gnawing, dull pressure or pain. About a third of the patients report distress coming on within the first half hour after eating, while a third have distress from one to three hours after eating. Two-thirds obtain relief with alkali treatment and one-third with food.

About half the patients with hypertrophic gastritis show periodicity of distress. As in those with the superficial variety, the distress is localized in the upper portion of the abdomen, in the epigastrium chiefly. The distress is likely to be severe pain, perhaps in 25 per cent of the patients. The rest report dull, burning or gnawing pain or pressure, not often coming on soon after eating but usually beginning from one to three hours later. About 50 per cent of the patients obtain relief by taking food or alkali.

We fully realize that similar symptoms occur in patients without chronic gastritis or any other demonstrable disease of the stomach or other organs. Among one hundred patients who were gastroscopically normal and who had no demonstrable disease of any other kind, four presented complaints, of which the following history and findings are typical:

J. W. H., a man aged 25 years, reported that epigastric burning developed three years previously, usually being present in the morning when he arose, when hot water aggravated the distress. It was relieved, however, almost at once by a full breakfast. Burning recurred from two to four hours after eating and was always relieved by a full meal. Marked belching, occasional bloating and borborygmi were noted but were not distressing. Stools were passed twice daily and were soft and formed. No catharsis or enemas were used. There had been short periods of headache and constipation three years earlier, but these were no longer present. No other symptoms or illness of note was recorded. Physical examination revealed no abnormality, except slight diffuse abdominal tenderness.

The blood, urine and stools were normal. The Ewald test showed free hydrochloric acid of 8 and total acid of 28. Roentgenographically the esophagus, stomach, duodenum and colon were normal.

Gastroscopic Examination.—The whole stomach was seen and appeared entirely normal.

Diagnosis.—The clinical diagnosis was chronic functional colitis. On reviewing this case we are of the opinion that this clinical diagnosis was not justified.

The predominance of men with hypertrophic gastritis is noted in this small group as well as in earlier reports (Schindler, Henning and others). Though not explained, this predominance may afford a clue in the future as to etiology.

The degree of gastritis or extent of gastric involvement bore no regular relationship to the type, severity or frequency of distress in these patients.

Antral gastritis, namely, gastritis confined to the antrum, was noted in only two of the patients included in this report, both of them with the hypertrophic type of gastritis. The marked discrepancy in frequency of antral gastritis between gastroscopic findings on the one hand and surgical material (resection) on the other is again noted though not explained.

In conclusion, we feel justified in stating that until more general use of the gastroscopic method is adopted and numbers of experienced gastroscopists are available, until there is more definite recognition of symptoms actually due to chronic gastritis in its various forms, until more active treatment designed not only to cure symptoms but to ameliorate or cure pathologic conditions of the gastric mucous membrane is persisted in, until the results of treatment are checked as a routine by follow-up gastroscopy and until etiology becomes clearer,

chronic gastritis will remain an unclear clinical entity that will lure medical men on to further exploration. In spite of these limitations, however, chronic gastritis has regained a rightful place in the differential diagnosis of gastric pathologic conditions as a result of the development of a safe endoscopic method of examining the stomach.

SUMMARY

The histories of twelve patients with chronic superficial gastritis and twenty-three with chronic hypertrophic gastritis, selected from a group of three hundred and forty-nine patients, are presented in detail as to subjective symptoms and objective findings, including physical, laboratory, roentgenographic and gastroscopic study.

The patients selected for analysis presented no other demonstrable pathologic condition to account for the symptoms.

Four typical case reports are cited of patients with the two types of gastritis, as well as that of a patient with a typical history but with some other disease complicating the gastritis and one of a "normal" patient with similar complaints but without demonstrable disease.

Comment is made on the similarity and differences of histories in the chronic superficial and in the hypertrophic form, on the predominance of men with hypertrophic gastritis, on the lack of correspondence between the extent and severity of gastritis and the severity of symptoms and on the observation of only two patients in this group with gastritis limited to the antrum.

EFFECT ON THE ELECTRO-ENCEPHALOGRAM OF CERTAIN DRUGS WHICH INFLUENCE NERVOUS ACTIVITY

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The electro-encephalogram is analogous to the electrocardiogram; it is a record of the electrical potentials originating in the brain. Hans Berger [1] demonstrated the feasibility of "leading off" these potentials through the intact human skull and made records of them in various neurologic and pharmacologic conditions.

In work already published we [2] (together with Hallowell Davis) have reported the changes of electrical potential which accompany impaired consciousness, either when occurring spontaneously, as in petit mal, or when induced by means of syncope, anoxemia or hyperpnea. We now wish to report the changes resulting from the administration of various drugs. Our observations follow those of Berger [1c,h] as regards certain of the drugs and those of Loomis and Harvey [3] as regards acute alcoholism. Aside from these authors we know of no one who has studied the effect of drugs on the electro-encephalograms

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1. Berger, Hans: (*a*) Ueber das Elektrenkephalogramm des Menschen, Arch. f. Psychiat. **87**:527, 1929; (*b*) J. f. Psychol. u. Neurol. **40**:160 (May) 1930; (*c*) Arch. f. Psychiat. **94**:16, 1931; (*d*) **97**:6, 1932; (*e*) **98**:231, 1932; (*f*) **99**:555, 1933; (*g*) **100**:301, 1933; (*h*) **101**:452, 1933; (*i*) **102**:538, 1934; (*j*) **103**:444, 1935; (*k*) **104**:678, 1936; (*l*) Ueber die Tätigkeit des menschlichen Grosshirns, München. med. Wchnschr. **80**:844 (June 2) 1933; (*m*) Das Elektrenkephalogramm des Menschen, Med. Welt **7**:928 (July 1) 1933; (*n*) Das Elektrenkephalogramm des Menschen und seine Bedeutung für die Psychophysiologie, Ztschr. f. Psychol. **126**:1, 1932.

2. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

3. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Electrical Potentials of Human Brain, J. Exper. Psychol. **19**:249, 1936.

of human beings. Various workers have, however, carried out experiments on animals which bear directly on this subject, notably Adrian,[4] Bremer,[5] Range[6] and Derbyshire[7] and their associates.

In our experiments small metal electrodes were cemented to the scalp and to the lobe of the ear. The electrode on the scalp was connected to the grid of a capacity-coupled vacuum tube amplifier having a gain of about ten million; the ear electrode was connected to ground. Records were made on paper with an ink-writing oscillograph capable of registering frequencies up to 40 per second. When it seemed of interest to compare the simultaneous activity from different parts of the head, additional electrodes were cemented to appropriate points on the scalp, and each was connected to the grid of an amplifier similar to the one just referred to. The ear was used as a common ground for all channels of amplification. Our equipment allowed the simultaneous recording of activity from four parts of the brain. Control tracings were obtained for a period of from fifteen to thirty minutes before the drug was given, and the record was continued after the maximum clinical effect of the drug had been obtained. Both normal subjects and patients were used. The subject sat in a comfortable chair or lay in a hospital bed. In all, eighty-four experiments were carried out with twenty drugs.

In the normal waking subject the potentials which can be led off from the head have a voltage of from ten to seventy-five millionths of a volt or about one one hundredth of the voltage recorded in the electrocardiogram. For purposes of orientation, figure 1 is shown. This is a short segment of the record of a normal subject. The most prominent rhythm is 10 a second, seen best in the occipital region and usually influenced greatly by the opening and closing of the eyes and by what, for want of a better term, must be called attention. With the eyes closed, the 10 a second rhythm is prominent; with the eyes open, it temporarily disappears, and, in general, any concentration of attention tends to abolish this rhythm. In some persons, however, the 10 a second rhythm does not appear at all; in others it continues even when the eyes are open. Adrian[8] and Jasper[9] have shown that the pattern of the

4. Adrian, E. D., and Matthews, B. H. C.: The Interpretation of Potential Waves in the Cortex, J. Physiol. **81**:440, 1934.

5. Bremer, F.: Action des différents narcotiques sur les activités électriques spontanée et réflexe du cortex cérébral, Compt. rend. Soc. de biol. **121**:861, 1936.

6. Range, R. W.: Der Einfluss von Narkotika auf die Tätigkeit der Grosshirnrinde des Kaninchens, J. f. Psychol. u. Neurol. **46**:364, 1935.

7. Derbyshire, A. J.; Rempel, B.; Forbes, A., and Lambert, E. F.: The Effects of Anesthetics on Action Potentials in the Cerebral Cortex of the Cat, Am. J. Physiol. **116**:577, 1936.

8. Adrian, E. D., and Yamagiwa, K.: Origin of Berger Rhythm, Brain **58**:323 (Sept.) 1935.

9. Jasper, H. H., and Andrews, H. L.: Human Brain Rhythms: I. Recording Technique and Preliminary Results, J. Gen. Psychol. **14**:98, 1936.

potential fluctuations differs for various areas of the cortex. The work of Hallowell Davis [10] indicated that the pattern of any person, like his signature, is, within limits, characteristic and constant. Furthermore, the records of identical twins are similar, an observation which suggests an inherent biologic significance in the rhythms portrayed in the electro-encephalogram.

Any observed rhythm presumably represents the sum total of the changes of potential of various discharging units in the region of the brain beneath the stigmatic electrode. Certain procedures, such as opening the eyes or increasing the attention, cause a flattening of the waves, presumably by a "canceling out" process. In some conditions, such as death, deep asphyxia and postepileptic stupor, the flatness of the record undoubtedly represents a decrease in the total electrical activity of the

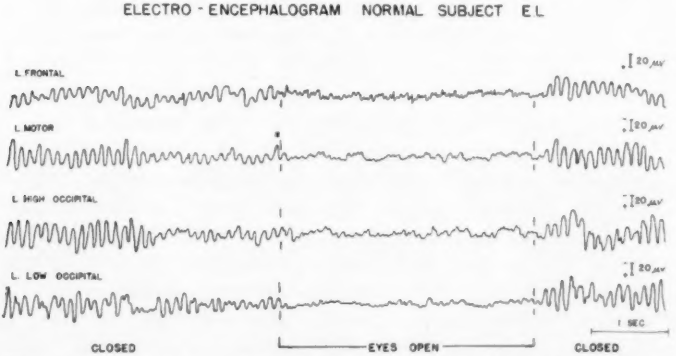

Fig. 1.—The electro-encephalogram of a normal subject with eyes closed and open. The four curves are simultaneous records of potential fluctuations from four different parts of the head, as labeled. The deflection caused by a signal of known sign and voltage is shown at the right of the figure. The speed of the paper is indicated by the one second time calibration in the lower right corner of the figure (also in figures 2 to 7). At the bottom of the chart are shown the periods during which the eyes of the subject were open and closed.

brain suggestive of a discharged battery. An increase in voltage may mean more units discharging synchronously or a greater discharge from each single unit, or both conditions may obtain. What these discharging units are is not known; but because the type of activity seen in the electro-encephalogram is best obtained from masses of gray substance, the assumption seems reasonable that the structures responsible are cell bodies or synapses.

10. Davis, H., and Davis, P. A.: Action Potentials of the Brain in Normal Persons and in Normal States of Cerebral Activity, Arch. Neurol. & Psychiat. **36**:1214 (Dec.) 1936.

RESULTS

We shall first cite the results obtained with drugs the administration of which was followed by significant changes in the electro-encephalogram.

Scopolamine.—Scopolamine or atropine was given in three cases, in doses of from $\frac{1}{100}$ to $\frac{1}{50}$ grain (0.6 to 1.3 mg.) intravenously. After the injection there was at first a decrease in the voltage of all waves (a change characteristic of drowsiness), and then bursts of regular waves of high voltage appeared with a frequency of about 10 a second. These bursts came rather regularly at about ten second intervals

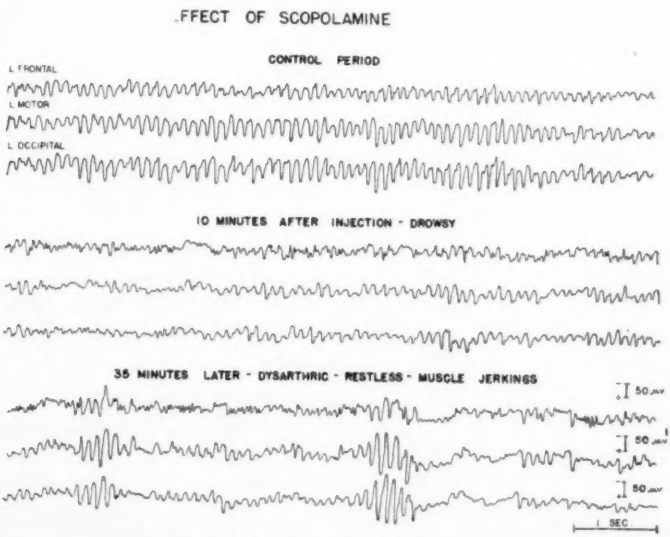

Fig. 2.—The effect of the intravenous injection of 1/50 grain (1.3 mg.) of scopolamine. Simultaneous tracings from three areas of the skull (left frontal, left motor and left occipital) are shown. The first trio of simultaneous curves was made in the control period before scopolamine was injected. The second trio was made ten minutes after the injection, when the patient was somewhat drowsy; the third trio was made thirty-five minutes later, when speech was dis-articulate and the patient was having involuntary twitchings of muscle groups every few seconds. The large, slow fluctuation in the last three records correlated with the involuntary muscular movements.

and lasted from one to three seconds. During this type of activity the patient was not asleep. In the experiment in which we gave a dose of scopolamine sufficient to produce muscular twitching ($\frac{1}{50}$ grain, 1.3 mg.), the twitches coincided with unusually large bursts of these high voltage, 10 a second waves. Figure 2 is the record of this experiment.

Morphine.—One-fourth grain (16 mg.) of morphine sulfate was given intravenously to each of three subjects. As with scopolamine, the waves of the electro-encephalogram became somewhat flatter, and the record was interspersed with bursts of high potential, 10 a second waves. One epileptic patient regularly had, during sleep, abnormal sharp spikes in the record taken from the frontal area of the brain. Injection of morphine caused these abnormal spikes to appear (even though the patient was not asleep at the time).

Barbiturates[11] *and Sodium Bromide.*—The effects of various barbiturates and sodium bromide on the normal electro-encephalogram were much alike. Soluble phenobarbital U. S. P. (phenobarbital sodium) was given fourteen times (5 to 10 grains [0.3 to 0.6 Gm.] intravenously). When sleep or drowsiness was not induced, there was no detectable change in the normal electro-encephalogram. When the injection was followed by drowsiness, the record usually flattened as in natural drowsiness; if sleep occurred, the record closely resembled that obtained during normal sleep; that is, large, slow waves appeared, and a new frequency of approximately 14 per second (which is rare in waking states) appeared in bursts (fig. 3).

These statements are true also for sodium bromide, which was given intravenously to eight subjects, 30 grains (2 Gm.) to each. In the cases in which a maximum effect was shown, the slow waves became slower, and the bursts of fast activity became less numerous; that is, there was an exaggeration of the changes seen during sleep.

In addition to observations of persons with normal electro-encephalograms given phenobarbital and sodium bromide, we made them on patients having frequent abnormalities of rhythm, which we believe are diagnostic of epilepsy. Records depicting the effect of anticonvulsants on the wave formation which is typical of petit mal seizures have been published elsewhere.[12] Both these drugs acted either to prevent the appearance of abnormal rhythms or to disrupt and shorten them. Petit mal seizures, which before were visible to the observer, now were detectable only by the electro-encephalograph. One patient who showed abnormal waves during natural sleep had them also in even increased number during sleep induced by these anticonvulsant drugs.

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11. The phenobarbital, evipal (N- methylcyclohexenylmethylmalonylurea) and chemical homocamfin (methylisopropylcyclohexone) used in these studies were supplied by the Winthrop Chemical Company; the ergotomine tartrate was supplied by the Sandoz Chemical Works.

12. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. **36**:1236 (Dec.) 1936.

Evipal (N-methylcyclohexenylmethylmalonylurea) or pentobarbital sodium was given intravenously to six subjects in doses of from 2 to 8 grains (0.13 to 0.5 Gm.). When the larger amounts were used, the injection was given slowly, the subject counting the while so that the various stages of anesthesia could be correlated with the pattern of the electro-encephalogram. With increasing drowsiness of the subject, the rhythm changed, until at the stage of surgical anesthesia the slow waves were at a frequency of only 1 or 2 a second and the 10 a second activity was represented only by the jagged, irregular contour of the slow waves. It should be pointed out, however, that in the early stages of anesthesia, while the patient was still sufficiently conscious to count

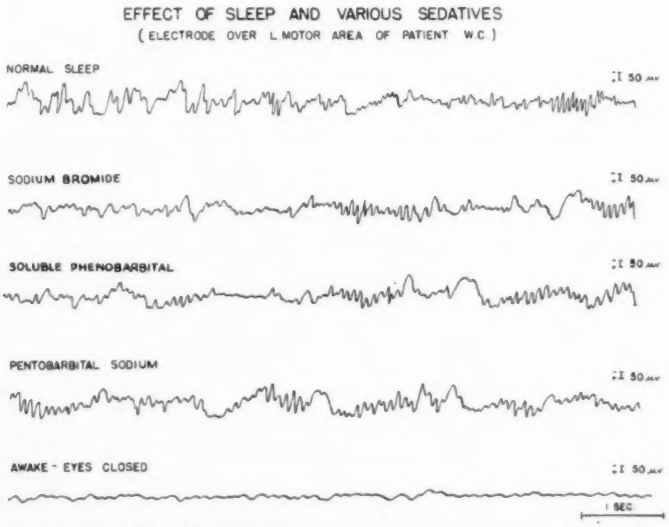

Fig. 3.—The effect of sleep and of various sedatives given on different occasions to the same subject. The curve at the bottom of the chart was a control record with the patient awake and the eyes closed. The record at the top was made when the patient was soundly asleep. The three remaining records were made after the intravenous injection of 30 grains (2 Gm.) of sodium bromide, 10 grains (0.65 Gm.) of soluble phenobarbital U. S. P. (phenobarbital sodium) and 4 grains (0.26 Gm.) of pentobarbital sodium, respectively. In each instance the patient was asleep. The similarity of the records of induced and of natural sleep is obvious.

(fig. 4), there was a great increase in the voltage of all the components of the normal electro-encephalogram. This increase in voltage persisted but became intermittent as unconsciousness supervened; i. e., the steady

high voltage was broken up into bursts of activity. These bursts became farther and farther apart as the anesthesia progressed, and large, slow waves, about 1 or 2 per second, appeared.

When doses are used that are just sufficient to induce sleep, the curve may be indistinguishable from the person's record during ordinary sleep. The various sedatives which we have used all produce comparable changes in the electrical activity of the cortex. Figure 3 is the record of a subject who was given intravenous injections of various sedatives on different occasions. At the bottom is a sample of his waking record. The similarity is obvious between this patient's record taken during ordinary sleep and the record taken during sleep which followed the intravenous injection of a sedative.

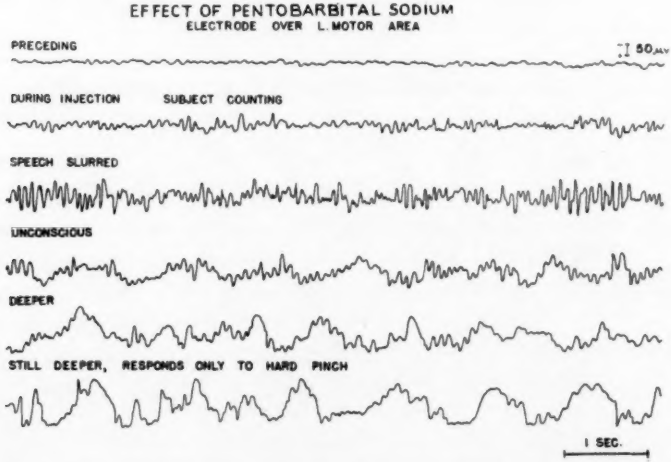

Fig. 4.—The effect of intravenous injection of pentobarbital sodium. All the records in this figure were from the left motor area. The top strip was made during a normal control period before an injection was given. Subsequent strips were taken at various intervals during and after the injection. The second and third strips were made when the patient was counting, and the fourth strip was made when he had ceased to count and did not respond to questions. The bottom strip is from the record made when he was in a state of light surgical anesthesia, responding only to painful stimuli.

Ether and Alcohol.—Anesthetization by inhalation of ether was produced in three subjects, and mild intoxication with alcohol (induced by the ingestion of 30 or 40 cc. of 95 per cent alcohol) was studied in three subjects. One intoxicated person was secured from the accident ward. A study of the records obtained from intoxicated patients indicates that ether and alcohol produce changes in the electro-encephalogram

which are altogether comparable. These changes have a general similarity also to those produced by the barbiturates and by anesthesia induced by pentobarbital and evipal, though there are certain characteristic differences. The barbiturates in soporific doses may produce at first flattening as in natural drowsiness and then a great increase in the voltage of those frequencies, which are around 14 per second; the first effect of alcohol and ether, on the other hand, is to increase the voltage of those frequencies which are around 20 per second and at the same time to diminish the voltage of frequencies around 10 per second. This occurs while the subject is still conscious. As consciousness is lost, these high voltage, fast waves disappear and high voltage, slow waves with a frequency of about 5 per second take their place. As unconsciousness becomes more and more profound, the slow waves become slower and slower. In ether anesthesia when a "surgical level" is reached, the slow waves have a frequency of about 1 per second (fig. 5). Superimposed on these are small, faster waves with a frequency of 10 or 20 per second, so that the slow waves have a crenated appearance. A practical application of these observations might be the use of the electro-encephalogram as a measure of the depth of anesthesia during surgical operations. The anesthetist and surgeon could have before them on tape or screen a continuous record of the electrical activity of both heart and brain.

A somewhat similar sequence of events is present in alcohol intoxication. The first record in figure 6 was taken when the patient was "dead drunk," unresponsive to any but painful stimuli. The second tracing is representative of the record taken ten hours later, when he was awake and able to talk intelligibly, but his manner and his sullen, suspicious attitude were abnormal. The third tracing was made seven hours later, when he appeared normal. As with ether, the largest waves (with 10 or 20 per second waves still visible) came with deepest unconsciousness.

COMMENT

Our findings are in general in accord with those of other workers who have studied the effect of the same drugs. Berger [1c] studied morphine and the barbiturates particularly. At no point do we disagree with his findings. The report of Loomis, Harvey, and Hobart on a case of acute alcoholism differs from ours by its failure to mention the presence of large, slow waves. Adrian's [4] records of ether anesthesia in animals are similar to ours, as are those of Bremer [5] and Derbyshire, Rempel, Forbes and Lambert [7] on the effect of ether and the barbiturates on animals. Range [6] also worked with ether on animals and reported the same type of alteration that we have described.

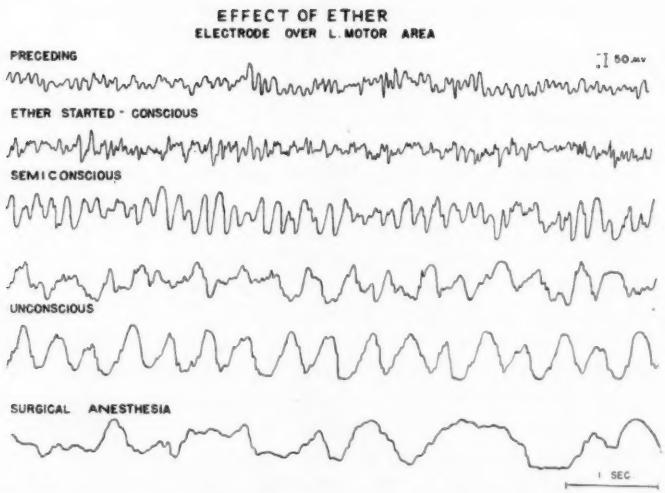

Fig. 5.—A record made during inhalation of ether. As in the preceding figure, the electrode was over the left motor area. The top strip was made when the patient was awake with eyes closed; the second shows the change that occurred when etherization was started but while the patient was fully conscious. In the third and fourth strips consciousness was progressively lessened and in the fifth the patient was unconscious. In the bottom strip he was in a state of surgical anesthesia, not responding to painful stimuli.

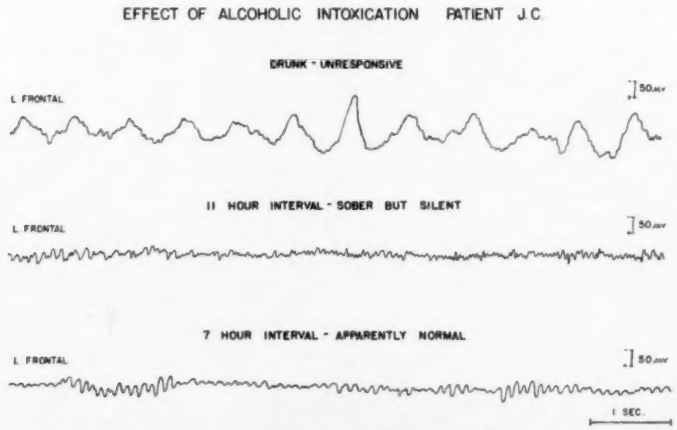

Fig. 6.—The effect of alcohol intoxication. In this instance the first strip was taken from a record made when the patient was drunk and unresponsive to any but painful stimuli. The middle strip is from a record taken eleven hours later, when he could be called sober but when he was unnaturally silent and morose. The bottom strip shows the change that had occurred seven hours later, when the patient was normal.

A number of drugs which we tried did not have any appreciable effect on the electro-encephalogram, at least in the doses given. The following list of these drugs gives the doses used and the number of experiments. Administration was by the intravenous route, except that sodium nitrite was given by mouth, pitressin intramuscularly and trichlorethylene by inhalation.

Obviously, for conclusive demonstration the number of observations with some of the drugs in this list would need to be increased.

The presence of strychnine in this group may seem strange in view of the animal experiments of Fischer [13] and of Kornmüller,[14] in which increased electrical activity was recorded after the administration of strychnine. However, these experimenters used amounts of strychnine sufficient or nearly sufficient to induce convulsions. We used only $\frac{1}{60}$ to $\frac{1}{10}$ grain (1 to 6 mg.) intravenously, an amount insufficient to induce motor symptoms.

	Dose	No. of Experiments
Epinephrine hydrochloride	0.5 to 0.8 mg.	6
Benzedrine sulfate	10 mg.	3
Caffeine with sodium benzoate	0.5 Gm.	3
Cibalgine (aminopyrine and dial)	0.25 Gm.	3
Cobra venom	1 cc.	1
Ergotamine tartrate	0.5 mg.	6
Histamine	0.5 cc.	2
Pitressin (after 2 liters of water)	1 cc.	2
Sodium nitrite	0.3 to 0.5 Gm.	2
Strychnine sulfate	1 to 10 mg.	6
Trichlorethylene	1 cc.	1

In five of the eight instances in which ergotamine tartrate was used, the subjects were experiencing migraine headache, which was completely relieved by the injection. Two of these electro-encephalographic records showed significant changes. We intend to pursue this subject further.

Explanation is needed also regarding our negative results with camphor. Amounts insufficient to produce symptoms did not alter the rhythm, but in four instances an intravenous dose (0.5 to 1 cc.) of a preparation of camphor, homocamfin (methylisopropylcyclohexone), given to a patient with epilepsy was followed by a generalized convulsion. Approximately twenty seconds after the homocamfin was injected, the voltage of the waves became greater. Parenthetically, this method affords a means of measuring circulation time from the vein of the arm to the cortical cells of the brain. The potentials continued to

13. Fischer, M. H.: Elektrobiologische Auswirkungen von Krampfgiften am Zentralnervensystem, Med. Klin. **29**:15, 1933.

14. Kornmüller, A. E.: Der Mechanismus des epileptischen Anfalles auf Grund bioelektrischer Untersuchungen am Zentralnervensystem, Fortschr. d. Neurol., Psychiat. **7**:391 (Sept.); 414 (Oct.) 1935.

increase in voltage (though without clinical evidence of seizure) until finally, after a lapse of about thirty seconds, the patient had a psychomotor attack (fig. 7). It seems probable that any drug capable of producing convulsions, if given in a convulsing dose, will cause disturbances in the normal electrical activity of the brain comparable to the disturbances seen when a spontaneous epileptic seizure is recorded.

Probably a similar statement applies to drugs capable of producing sleep. Marked variations from the normal electro-encephalographic tracing are seen only in association with convulsions (or involuntary movements), sleep or stupor. Gross alterations of the electro-encephalogram likewise are seen after the administration of only those drugs which produce convulsions (involuntary movements), sleep or stupor;

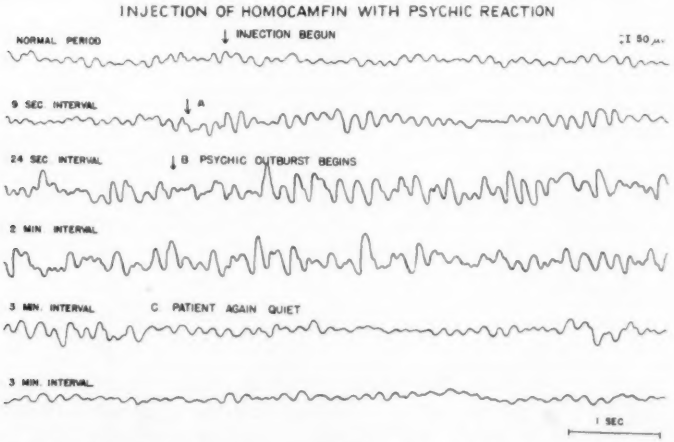

Fig. 7.—The effect of an intravenous injection of 1 cc. of homocamfin. The top strip is from the patient's normal record with eyes closed. Intravenous injection of the drug was begun at the point marked by the arrow. A nine second interval separated the first and second strips. At the arrow marked *A*, which indicates a point sixteen seconds after the injection was started, the first effect of the drug on the potentials can be noted. At *B* in the third curve, which indicates a point forty-seven seconds after the beginning of the injection, the subject began to have a mild psychic outburst, which continued for a little more than five minutes. During this period he was emotionally disturbed and did not reply to questions; he had no recollection of what took place after the episode was over. At the point marked *C* on the fifth curve he was again quiet and able to answer questions.

and these alterations do not occur unless a sufficient dose is given to produce one of these effects. In comparing two drugs we have found, in general, that the more nearly alike the effect of the drugs on the

involuntary muscular activity or on the consciousness of the patient, the more nearly alike the records obtained with the electro-encephalograph.

Aside from the effect of medication on the normal electro-encephalogram, we have observed the effect of certain procedures (inhalation of carbon dioxide and concentration of attention) which tend to alter both the normal rhythm and the rhythm in epilepsy and which inhibit seizures. These results have been presented elsewhere.[10]

In the present stage of study of the electrical activity of the brain we are primarily concerned with the securing of data, which must precede any attempt at interpretation of results. The administration of drugs which affect mainly the vegetative system (ergot, epinephrine and atropine) had little appreciable effect on the electrical activity of the cortex. When drugs were used which did alter the electrical activity of the cortex, the activity of all regions from which we led off was modified. It is possible that careful study might show that changes developed in one area before they did in another or that alterations were greater in a certain area. These are questions that can be adequately dealt with only if the investigation is not limited to the outer surface of the cortex but includes the deeper-lying gray masses, particularly the diencephalon. A discussion of the possible meaning of alterations such as those which we have described is outside the scope of the present paper and will be dealt with elsewhere in conjunction with the interpretation of our findings in epilepsy.

SUMMARY

Observations on human beings have been made of the effect on the electro-encephalogram of twenty drugs known to affect the central nervous system. The most definite changes attend the use in effective doses of convulsants, sedatives and anesthetics. Drugs primarily affecting the autonomic nervous system produce no comparable changes.

Sedatives cause changes similar to those observed in normal sleep. In place of the fast and rather steady activity characteristic of the waking state, there are slow, large voltage fluctuations, with occasional bursts of fast activity and also short periods in which there are almost no fluctuations. If sedation is so heavy that the patient cannot be aroused, the bursts of fast activity disappear, and the slow components become slower, of larger voltage and almost continuous. Ether produces, first, a decreased voltage of the lower frequencies in the normal record and an increased voltage of the higher frequencies and, later, large voltage, slow waves with a 10 a second rhythm superimposed. Electro-encephalography may therefore be of value in controlling depth of anesthesia and sedation. Alcohol is similar in its effect to ether.

Convulsants produce large voltage disturbances such as are seen in epileptic seizures; the frequency may be fast or slow. In patients having frequent petit mal seizures, bromide or phenobarbital in doses insufficient to change normal electrical activity prevents or disorganizes the pattern of the discharges which characterize the seizure.

CONCLUSIONS

Only those drugs which were given in sufficiently large doses to cause impairment of consciousness or involuntary muscular movements produced marked alterations in the electro-encephalogram.

Drugs which cause a sleeplike state altered the electro-encephalogram in the same general way as natural sleep.

Drugs which cause a profound abolition of consciousness produced records similar to those seen in stupor from whatever cause.

Drugs which cause convulsions resulted in alterations of electrical activity similar to those which occur in the convulsions of epilepsy.

The more nearly alike the clinical action of two drugs, the more nearly alike are the changes which they produce in electro-encephalograms.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

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EXPERIMENTAL GLOMERULONEPHRITIS

The past year has been characterized by marked progress in attempts to produce glomerulonephritis experimentally. These attempts have been recently reviewed by Masugi,[1] who was one of the earliest to achieve experimental glomerulonephritis; by Ahlström,[2] and by Smadel.[3] All of these workers have utilized cytotoxic serum in its production.

Ahlström [2] began by investigating the action of Dick toxin, finding that it had a weak nephrotoxic action and produced only a few focal degenerative changes when injected into the renal arteries of normal rabbits or of rabbits which had been previously sensitized to Dick toxin.

Ahlström found also that when serum was injected into the renal arteries of sensitized animals most of them showed only perivascular cell infiltrates, frequently localized about the afferent glomerular artery, in which occasionally hyaline thrombi were observed and in some instances slight glomerular changes as well. When, however, animals which had been sensitized to horse serum were given preliminary injections of a staphylococcus toxin, subsequent injections of serum gave a different result. The changes which then ensued were notably glomerular and appeared in the form of an intracapillary reaction. It is also noteworthy that in some animals so treated thrombi of fibrin were found in the capillaries of the liver, with acinar necrosis and bleeding, suggestive of the hepatic lesions of eclampsia of pregnancy. These experiments led

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1. Masugi, M.: Die Pathogenese der diffusen Glomerulonephritis im Lichte experimenteller Erzeugung dieser Nierenerkrankung bei Tieren, Zentralbl. f. inn. Med. **56**:417 (May 11) 1935.

2. Ahlström, C. G.: Zur Pathogenese der akuten diffusen Glomerulonephritis. Experimentelle Untersuchung über die allergische Gewebsreaktion der Niere, Acta path. et microbiol. Scandinav., supp. 29, 1936, p. 1.

3. Parks, A. E., and Taussig, B. L.: Reaction of Sensitized Dog's Kidney to Horse Serum Injected into Renal Artery, Proc. Soc. Exper. Biol. & Med. **34**:889 (June) 1936.

Ahlström to conclude that in order to produce glomerulonephritis experimentally it is necessary to have both a general allergic hypersusceptibility and an organ-predisposing factor. His failure to produce significant lesions in sensitized animals by the injection of horse serum alone is borne out by similar experiments by Parks and Taussig.[3]

Smadel [4] has made extremely important observations on the production of nephritis experimentally with nephrotoxic serum. In producing the serum he found that even with careful preliminary perfusion of the antigenic kidney the resulting serum contained substances other than pure renal cytotoxins. Pure nephrotoxic effects were produced in rats only when other antibodies had been absorbed from the serum and when the rats had been desensitized to the antirat serum of rabbits. The pure nephrotoxic effects consisted of proteinuria and cylindruria, azotemia and anasarca but no hematuria. Hematuria and associated glomerular changes occurred when anaphylactoid factors were present and did not occur if these factors were absorbed or if the animals were desensitized.

Smadel found the nephrotoxic factor to be absorbed by renal cells, by fat-free renal substance and to some extent by hepatic cells and fat-free hepatic substance. It was not absorbed by lipids from the kidney, liver or brain or by red blood corpuscles or serum. It was all found to be present in the globulin fraction of the serum. Such serum is relatively organ specific. Smadel finds it difficult to desensitize against the nephrotoxic factor so as to produce reverse anaphylaxis.

The course of the experimental nephritis thus induced has been studied by Farr and Smadel,[5] who have devised ingenious methods for obtaining blood from rats and for collecting urine from them for determination of the urea clearance. Farr has previously described micromethods for the determination of urea and ammonia. By these methods they have established the normal values of urea clearance for rats.

NEPHRITIC HYPERTENSION

Interest seems to have been renewed in vasopressor substances arising in the kidney or in pressor effects originating in those organs. Govaerts and Dicker [6] report the finding of a vasopressor substance

4. Smadel, J. E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum, J. Exper. Med. **64**:921 (Dec.) 1936.

5. Farr, L. E., and Smadel, J. E.: The Urea Clearance of Rats: Its Technique and Normal Range, Am. J. Physiol. **116**:349 (July) 1936.

6. Govaerts, P., and Dicker, E.: Production intrarénale de substances hypertensives par ligature ou pincement de l'artère rénale, Compt. rend. Soc. de biol. **122**:809, 1936; Les substances vasopressives présentes dans le sérum des néphrétiques hypertendus existent-elles dans le sérum des sujects normaux? ibid. **122**:807, 1936.

in the kidney of a dog when the renal artery was partly closed with a clamp. In such a case alcoholic extracts of the animal's blood and of the partly ischemic kidney exerted a strong vasopressor effect on other dogs. When the artery to one kidney was kept ligated for several days, the pressor substance was found within that kidney, though none was found in the blood or in the other kidney.

That the mechanism of pressor effects from the injured kidney is not entirely humoral is shown by the studies of Arnott, Kellar and Matthew.[7] These authors observed that hypertension did not occur in oxalate nephritis if the kidneys were denervated, though it does occur if the nerves are intact. Injections of oxalate did not cause hypertension in nephrectomized animals. When unilateral nephrectomy was performed and the other kidney was denervated, hypertension did not follow the injection of oxalate. The authors point out, however, that the injury to the kidneys that is due to the oxalate is purely tubular. They report preliminary experiments on rabbits with experimental glomerulonephritis produced by a nephrotoxic duck serum. So far hypertension has not been observed in animals subjected to unilateral nephrectomy and denervation of the other kidney.

TOXEMIA OF PREGNANCY

Peters,[8] after a review of a considerable number of cases of toxemia of pregnancy, expresses the belief that "toxemia" does not occur de novo but represents an explosive reaction induced by pregnancy in women who have suffered from previous renal or vascular injury, such as pyelitis, pyelonephritis, nephritis or hypertension—in fact, any of the diseases which, outside of pregnancy, give rise to arteriolar disease, hypertension or functional impairment of the kidneys.

Peters has been unable to find any fundamental disorder of metabolism underlying toxemia of pregnancy. Studies of blood chemistry or metabolism have thrown surprisingly little light on the subject. Peters believes that during pregnancy preexisting renal or vascular disorders of a benign nature may suddenly burst into a malignant state. Since the frequency of toxemia exceeds greatly the incidence of renal and vascular disease in nonpregnant women of comparable age, one must assume that the gravid state increases the sensitivity of the kidneys and vascular system to the action of the ultimate etiologic agents.

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7. Arnott, W. M.; Kellar, R. J., and Matthew, G. D.: The Experimental Pathology of Renal Hypertension, Edinburgh M. J. **43**:135 (Sept.) 1936.

8. Peters, J. P., and Zimmerman, H. M.: The Rôle of Pyelitis in the Production of Toxemias of Pregnancy, Tr. A. Am. Physicians **51**:287, 1936. Peters, J. P.; Lavietes, P. H., and Zimmerman, H. M.: Pyelitis in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **32**:911 (Dec.) 1936. Peters, J. P.: The Nature of Eclampsia, Yale J. Biol. & Med. **9**:233 (Jan.) 1937; Toxemias of Pregnancy, ibid. **9**:311 (March) 1937.

Peters dismisses pituitary basophilia as a causative factor in toxemia of pregnancy, since it is found in patients with hypertension from a variety of causes; hence it may be regarded simply as a mechanism by means of which the organism raises the blood pressure in response to a variety of impulses. Whether or not Peters is justified in such a summary dismissal of this factor, he has at least directed thought and inquiry concerning toxemia along new lines. If his views prove ultimately to be correct, he will have raised new issues concerning the prevention of toxemia of pregnancy.

PROTEINURIA

Bing [9] has prepared an excellent historical review of both early and recent work concerning the origin of the urinary proteins. Using creatinine clearance as a relative measure of the rate of glomerular filtration, he finds that the total protein and the albumin content of the urine vary with the creatinine clearance. He finds that the ratio of the protein content of the urine to the creatinine concentration index has a constant value under constant experimental conditions in a given patient, though the values vary for different persons, since they must depend on individual filtration values and on the state of permeability of the glomerular membrane. Parallelism was also found to exist between urea excretion and proteinuria and to some extent cholesteroluria. He observed, as others have also, that proteinuria generally increases in persons on high protein diets. The latter observations led him to the conclusion that the change in protein content of the diet in some way alters the permeability of the glomeruli, a somewhat questionable conclusion, since it leaves out of account the probable changes in renal blood flow.

Since Bing finds evidence that the tubules function perfectly in nephrosis, he renews the suggestion, previously made by others, that the histologic appearances of the renal tubules, which are conventionally described as "degenerative changes," are simply due to the presence of small quantities of protein (and lipoids) which have made their way into the tubular cells during protracted periods of a high degree of proteinuria.

SERUM PROTEIN

Two recent studies have been concerned with the nature of the serum protein in nephrosis. Goettsch and Reeves [10] prepared precipitins for the protein of normal serum, which precipitate protein almost

9. Bing, J.: Studies on Proteinuria, "Albuminuria," Acta med. Scandinav., supp. 76, 1936, p. 1.

10. Goettsch, E., and Reeves, E. B.: Observations on the Nature of Serum Proteins in Nephrosis, J. Clin. Investigation **15**:173 (March) 1936.

quantitatively from such serum. When these precipitins were applied to serum of patients with nephrosis, both the albumin and the globulin fraction failed to precipitate completely. While the patient was convalescing from nephrosis the protein of the serum resumed its normal relation to precipitins.

In acute hemorrhagic nephritis the serum protein was precipitated in a normal manner.

Goettsch and Reeves also used globulin from serum of nephrotic subjects to stimulate antibody formation in rabbits. The antiserum thus formed was found to be not identical with that formed against the globulin from normal serum.

Alving and Mirsky [11] have also found that the albumin fractions of the blood and urine of nephrotic subjects differ from normal. When the globulin fraction was precipitated the remaining protein was found to consist in part of normal serum albumin and in part of a protein which contained far less cystine than the albumin of normal serum. On the other hand, when the urinary globulin was precipitated the remaining protein contained more cystine than the corresponding fraction in the plasma of nephrotic subjects but less than normal serum albumin. From this the authors conclude that the plasma albumin in nephrosis contains a substance with a low cystine content which passes through the kidney less readily than does normal serum albumin.

Wies and Peters [12] have reexamined the relation of serum protein to osmotic pressure and by statistical methods have derived equations for prediction of osmotic pressure from the protein analyses. They have found that the factors for albumin and globulin are of the same order of magnitude as those determined by Govaerts and von Farkas. They are not, however, proportionate to the commonly accepted values for the molecular weights of these proteins. Wies and Peters believe that calculations of the osmotic pressure from reliable analytic data are as likely to be accurate as attempts to measure it directly. Their data do not include any for patients with a high globulin (chiefly euglobulin) value, such as is found in association with myeloma and lymphosarcoma, so that their formulas should not be applied in cases of these conditions.

PLASMA LIPIDS

Page, Kirk and Van Slyke [13] have studied the plasma lipids in the chronic active stage of hemorrhagic Bright's disease, in which the

11. Alving, A. S., and Mirsky, A. E.: The Nature of the Plasma and Urinary Proteins in Nephrosis, J. Clin. Investigation **15**:215 (March) 1936.

12 Wies, C. H., and Peters, J. P.: The Osmotic Pressure of Proteins in Whole Serum, J. Clin. Investigation **16**:93 (Jan.) 1937.

13. Page, I. H.; Kirk, E., and Van Slyke, D. D.: Plasma Lipids in Hemorrhagic Nephritis, J. Clin. Investigation **15**:101 (Jan.) 1936.

urea clearance is above 20 per cent. In seven cases there was a definite tendency to hyperlipemia. As the disease passes into its terminal stages, it was found, there is a tendency for the level of the plasma lipids to decrease, and it may fall below the normal limits. The values for individual lipids, free cholesterol, cholesterol esters and phosphatides rise and fall together.

A similar study was carried out by these same investigators [14] for sixteen patients with uncomplicated essential hypertension, for none of whom the values for total plasma lipid or for any fraction of the lipid were in the least abnormal. These authors review the current ideas of the relation of hypercholesteremia to atheromatosis and hypertension, beginning with the work of Le Moine in 1911, which has met with varying support and denial by various investigators. In view of the negative findings of Page, Kirk and Van Slyke it appears that hypercholesteremia and elevation of the cholesterol-phosphatide ratio have nothing to do with arterial degeneration occurring in essential hypertension.

Page and Farr [15] have investigated the effects of diet and of the administration of thyroid on the lipids of the blood in nephrosis. The hyperlipemia of nephrosis and of chronic active glomerulonephritis is not influenced by the amount of fat in the diet or by the administration of thyroid. Whatever value thyroid may have in nephrotic states, its effects are not dependent on changes in the plasma lipids, and a high value for these substances should not be taken as a contraindication to liberal use of fat in the diet.

In contrast to the hyperlipemia accompanying the hypoproteinemia of nephrosis is the absence of hyperlipemia in states of malnutrition. Man and Gildea [16] report hypocholesteremia in such cases, usually associated with low values for total protein and albumin.

CLEARANCE TESTS IN RELATION TO GLOMERULAR FILTRATION AND RENAL BLOOD FLOW

In 1934 Van Slyke, Rhoads, Hiller and Alving [17] studied the relation of urea clearance and renal blood flow estimated from samples of blood

14. Page, I. H.; Kirk, E., and Van Slyke, D. D.: Plasma Lipids in Essential Hypertension, J. Clin. Investigation **15**:109 (Jan.) 1936.

15. Page, I. H., and Farr, L. E.: The Influence of High and Low Fat Diets and Thyroid Substance on the Plasma Lipids of Nephrotic Patients, J. Clin. Investigation **15**:181 (March) 1936.

16. Man, E. B., and Gildea, E. F.: Serum Lipoids in Malnutrition, J. Clin. Investigation **15**:203 (March) 1936.

17. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A.: The Relationship of the Urea Clearance to the Renal Blood Flow, Am. J. Physiol. **110**:387 (Dec.) 1934.

drawn directly from the renal vessels and demonstrated a marked parallelism between them. They found that dogs have a lower urea clearance when on low than when on high protein diets. This same effect of dietary protein on the urea clearance was observed by Farr [18] in a study of four children with nephrosis. The increase in clearance is due not to urea but to some other factor which probably increases the renal blood flow. Farr also noted that the creatinine clearance of these patients behaved in a similar manner.

The use of the creatinine clearance as a measure of the rate of glomerular filtration was first proposed by Rehberg. More recently the clearances of other substances, such as inulin and xylose, have been studied. Shannon and Smith [19] present the reasons for believing that no tubular activity is concerned in the excretion of inulin. They believe that xylose and sucrose are reabsorbed to some extent. The inulin clearance exceeds that of xylose by 22 per cent. When phlorhizin is given, the disparity between the values does not exceed 10 per cent. Shannon and Smith suggest the use of inulin as a measure of glomerular filtration, though they do not regard it as finally proved that inulin is not resorbed. Shannon [20] has found that when the value for creatinine in the plasma is low the ratio of creatinine clearance to inulin clearance is 1.39; when the value for plasma creatinine is high, the ratio is 1.12. These findings strongly support the belief that the excretion of creatinine may be influenced by tubular activity.

Simultaneous comparisons have been made by Landis, Elsom, Bott and Shiels [21] of the clearances of creatinine and certain organic compounds of iodine, skiodan, diodrast and hippuran. They found that the clearances of creatinine and skiodan were of the same order of magnitude. The clearances of diodrast and hippuran were greater than the creatinine clearance. In renal insufficiency hippuran clearance is reduced proportionately to the urea and creatinine clearances.

The excretion of phenolsulfonphthalein (phenol red) has been studied by Goldring, Clarke and Smith.[22] In normal men the phenolsulfonphthalein clearance is considerably larger than that of inulin, being

18. Farr, L. E.: The Effect of Dietary Protein on the Urea Clearance of Children with Nephrosis, J. Clin. Investigation **15**:703 (Nov.) 1936.

19. Shannon, J. A., and Smith, H. W.: The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, J. Clin. Investigation **14**:393 (July) 1935.

20. Shannon, J. A.: The Renal Excretion of Creatinine in Man, J. Clin. Investigation **14**:403 (July) 1935.

21. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E. H.: Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, J. Clin. Investigation **15**:397 (July) 1936.

22. Goldring, W.; Clarke, R. W., and Smith, H. W.: The Phenol Red Clearance in Normal Man, J. Clin. Investigation **15**:221 (March) 1936.

somewhat over three times as large with concentrations of dye in the plasma of less than 1 mg. per hundred cubic centimeters. Most of the phenolsulfonphthalein in the plasma is bound by protein. The fraction which is free varies directly with the total concentration of the dye. These authors estimate that not more than 6 per cent of the dye is excreted by glomerular filtration. Values for the phenolsulfonphthalein clearance are of the general magnitude of 400 cc. per minute of plasma and about 700 cc. per minute of whole blood. The authors point out that this corresponds well with the renal blood flow estimated from the normal urea clearance (about 75 cc.), which Van Slyke, Rhoads, Hiller and Alving [23] found to be about 10 per cent of the renal blood flow. Studies such as these inevitably revive interest in the possibilities of secretory activity of the tubules.

AGLOMERULAR TUBULES

In a previous review reference was made to the finding of aglomerular nephrons in contracted kidneys by Oliver and Luey, who speculated on the possibility of function in these tubular remnants kept alive by a blood supply from the vessels of Ludwig. In the course of a study of the vascular and parenchymal changes in the arteriosclerotic kidney Loomis [24] found adaptive changes in the vessels of Ludwig which bring them into great prominence as compared with their inconspicuousness in the normal kidney. Through such a vascular supply some tubules are preserved after occlusion of their glomerular supply, and in some cases tubular hypertrophy is noted. MacNider [25] also has drawn attention to aglomerular tubules in the kidneys of dogs with chronic renal disease produced by uranium. Long after the uranium injury the process of fibrosis and repair frequently obliterates glomeruli, yet tubules persist in a modified form, resembling those of the toadfish. MacNider suggests that the process of repair following degeneration is a reversion back to a type of structure normal for a remote ancestral form of kidney. It seems reasonable to believe that these well vascularized tubules are not without function, which in the severely damaged kidney may be of considerable importance.

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23. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A. S.: Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis: The Mechanism of Urea Excretion, Am. J. Physiol. **109**:336 (Aug.) 1934.

24. Loomis, Dorothy: Plastic Studies in Abnormal Renal Architecture: IV. Vascular and Parenchymal Changes in Arteriosclerotic Bright's Disease, Arch. Path. **22**:435 (Oct.) 1936.

25. MacNider, W. deB.: Pathological Changes in the Dog Kidney Resembling Normal Histological Structure in the Aglomerular Fish Kidney, Opsanus Tau, Proc. Soc. Exper. Biol. & Med. **31**:293 (Nov.) 1933.

RENAL RICKETS

Pappenheimer [26] reports that in young rats a reduction in amount of renal tissue regularly results in an increase in size of the parathyroid glands. When partially nephrectomized rats were maintained on a diet poor in calcium, growth was stunted, and the resulting skeletal changes were of far greater severity than those produced by the diet alone. The resulting changes corresponded closely to those of severe renal rickets in children. The animals showed hyperphosphatemia and azotemia, as in human beings with this disease.

MISCELLANEOUS REPORTS

Goldring and Graef [27] report observations made on two of three patients who died after the transfusion of incompatible blood. The kidneys showed a necrotizing process in the tubules resembling that seen in mercurial nephrosis. Pigment casts were conspicuous. There was considerable interstitial edema of the kidneys, which were large.

Schnitker and Richter [28] studied the renal lesions of fifty-five patients with gout. In seventeen instances nephritis was observed, predominantly of the vascular type. Only four postmortem examinations were made; three showed vascular lesions and one showed glomerulonephritis. In thirty-eight of the fifty-five patients no evidence of nephritis or functional impairment of the kidneys was discovered. These authors find vascular disease and hypertension to be more frequent in gouty persons than in normal persons of corresponding age. The renal lesions which occur are believed in the majority of instances to be secondary to vascular change and not to occasional deposits of urates in the kidneys, which apparently do not seriously affect renal function.

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26. Pappenheimer, A. M.: The Effect of Experimental Reduction of Kidney Substance upon the Parathyroid Glands and Skeletal Tissue, J. Exper. Med. **64**:965 (Dec.) 1936.

27. Goldring, W., and Graef, I.: Nephrosis with Uremia Following Transfusion with Incompatible Blood, Arch. Int. Med. **58**:825 (Nov.) 1936.

28. Schnitker, M. A., and Richter, A. B.: Nephritis in Gout, Am. J. M. Sc. **192**:241 (Aug.) 1936.

Book Reviews

Therapeutic Agents of the Pyrrole and Pyridine Group. By W. F. von Oettingen, M.D., Ph.D., Director of the Haskell Laboratory of Industrial Toxicology, Wilmington, Del. Cloth. Price, $4.75. Pp. 258, with 28 tables and 4 charts. Ann Arbor, Mich.: Edwards Brothers, Inc., 1936.

This book is the second in a series of monographs of the American Chemical Society. It is an important contribution to the pharmacologic literature. It consists of a systematic description, primarily pharmacologic but also chemical, of the substances the foundations of which are the pyrrole or pyridine nucleus that have been studied for their therapeutic activity. These two nuclei, which received their original interest and stimulus from coal tar chemistry, are the structural bases for many drugs. Among the accepted synthetic preparations may be mentioned isacen, neo-iopax, metycaine, diothane, eucaine hydrochloride and homatropine. Among the accepted alkaloids of plant origin may be mentioned physostigmine, sparteine sulfate, atropine, scopolamine, cocaine and pelletierine tannate. They also form the bases for a large number of substances both synthetic and occurring naturally which are either important structural units of tissues, such as the amino-acid tryptophan, or substances which have been extensively studied pharmacologically in both animals and man. These last-mentioned compounds, although they have not been shown to be sufficiently worth while to become accepted medicinal substances, are nevertheless important, because from this vast amount of effort will come other chemical substances worthy of acceptance. It is interesting to note that the substances derived from these two nuclei have actions in almost all fields of pharmacology, including local anesthetics, antiseptics and anthelmintics, and are concerned with the vegetative nervous system, smooth muscle, the circulatory, respiratory and excretory systems and the central nervous system.

Although the book was written from the standpoint of chemical constitution and pharmacologic action, the author points out that this view does not solve all the difficulties. There are other factors, such as physicochemical properties, which when better understood will undoubtedly lead to more rapid progress in the synthesis of new and useful drugs.

This book is primarily for pharmacologists, libraries and those persons interested in the particular subject. The chemical data, other than those showing the structural formulas, are not extensive. The latter are, however, handled beautifully. The inclusion of many tables is another desirable feature.

The book represents a commendable attempt to publish a small edition of a technical subject inexpensively. The photolithograph process has been used, with inexpensive but satisfactory paper, neatly bound in serviceable cloth. The type is large, clear and legible. It is hoped that this experiment in the publishing of valuable scientific material will be successful.

The Practice of Medicine. By Jonathan Campbell Meakins, M.D., LL.D. Price $10. Pp. 1,343, with 505 illustrations, 35 in color. St. Louis: C. V. Mosby Company, 1936.

One must welcome this new addition to the ever increasing number of textbooks on the practice of medicine. Physically the work is a substantially bound volume of 1,310 pages, exclusive of the index. There are 505 figures, an unusually large number, 35 of them being in color. To quote the author: "This is a pictorial age and many factual data are capable of graphic records. Therefore, I have diverted from the usual custom in text books on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description." The figures are aptly chosen to depict the important physical signs, microscopic and gross pathologic pictures, endocrine disturbances and roentgen findings fundamental to a complete and clear understanding of the problems.

This is particularly true of the colored plates, which illustrate, for the most part, the types of cyanosis, oral lesions, cutaneous tests, eruptions, smears of bone marrow and peripheral vascular phenomena. However, some of the conditions illustrated are so rare that it hardly seems advisable for them to occupy so much of the limited space assigned to a textbook on medicine.

The book has a decided British flavor. Chapter 1 opens with a consideration of the approach to the patient. Here and throughout the text symptoms are stressed. They represent, says Meakins, the earliest manifestations of disease and are therefore of primary importance. "They are clues to the clinical riddles. For this reason they have been given particular prominence, and where possible their causation has been described and their significance has been pointed out." The remaining twenty chapters deal specifically with descriptions of the diseases themselves, starting with diseases of the nasopharynx and mouth and continuing through the various systems and organs to diseases of nutrition, metabolism, parenteral infections, allergic diseases and diseases due to abnormal environment, chemicals and drugs.

Only such a prodigious worker as Meakins, with the broad understanding and knowledge of disease that he possesses, could attempt and execute so well a textbook of these proportions. Except for the chapters on diseases of the nervous system, urinary tract, endocrine glands and metabolism, the book represents his authorship alone. As one might suspect from Meakins' interest in research, the sections on respiratory and circulatory diseases, particularly with regard to the significance and interpretation of symptoms, are exceptionally lucid. One may find in this book, as in any book, points which one feels are not adequately stressed. For example, the recent work in England and the United States on the virus theory of influenza is entirely ignored, and the virus theory is barely mentioned. Dengue, which is again making its appearance as a significant disease in the southern part of the United States, is not mentioned in the differential diagnosis of influenza. However, the greatest inadequacy in the entire text, in the opinion of the reviewer, is in the consideration of renal disease. Here the mechanisms of the fundamental expressions of renal insufficiency are barely considered, and the relationship of vascular nephritis to other types is not clearly defined.

One must welcome this book for a thoroughness and completeness not always attendant on a book of this type and for the simplicity of plan and expression which convey to the reader a clear picture of the diseases described.

Dietetics for the Clinician. By Milton A. Bridges. Third edition. Price, $10. Pp. 1,055, with 85 tables. Philadelphia: Lea & Febiger, 1937.

While diet is, of course, of immense importance in medicine, there are only a few diseases—above all diabetes—in which accurate dietary prescriptions are necessary. Indeed, it is better as a rule to lay down simple principles rather than to burden the patient with detailed lists. The reviewer's main feeling on seeing this immense volume was therefore one of curiosity as to how it was possible to fill over a thousand pages in dealing with the subject; but a casual glance at the contents reveals promptly a great deal that is of questionable value. It is true that all the major considerations of diet are well presented, but the book would be better without the introduction of meaningless diet lists by the hundred for every possible condition. Under the heading of scurvy, for example, one is given not only a list of the foods containing vitamin C but a list of the foods which contain little or no vitamin C. Two pages are taken up with sample menus for patients with scurvy which, beyond the presence of citrus fruit, are meaningless. When one comes to the section on gastro-intestinal disease, it is hard to restrain one's impatience. Why, for example, should spinach and a whole page of other harmless foods be "omitted" by persons with visceroptosis, even admitting that the condition requires special clinical consideration? It is news to the reviewer that apple sauce and bread should be "omitted" by patients with renal glycosuria and that cake, fish and fresh bread are bad for those with indicanuria. Detailed diets for patients with cholecystitis with hyperacidity and cholecystitis with mucous

colitis, indeed with any condition from enuresis to influenza, are given in this monumental compendium under the section quaintly headed "Diseases and Their Diets." The best part of the book is that containing elaborate reference tables on the composition of foods, in which the subject is covered from every standpoint.

News and Comment

PAN AMERICAN MEDICAL ASSOCIATION

The *Queen of Bermuda* has been chartered for the Seventh Cruise-Congress of the Pan American Medical Association.

The main part of the congress will be held in Havana. Scientific sessions with operative clinics will be held on three days and will be divided into sections for the various specialties. This year there are four new sections, on tuberculosis, gastro-enterology, dentistry and industrial medicine. Meetings will be arranged with medical colleagues at the other ports of call.

The Hotel Savoy-Plaza in New York and the National Hotel in Havana will be the official hotels.

Applications for reservations should be addressed to the Pan American Medical Association, 745 Fifth Avenue, New York.

AMERICAN COLLEGE OF PHYSICIANS

The Twenty-Second Annual Session of the American College of Physicians will be held in New York, with headquarters at the Waldorf-Astoria Hotel, April 4 to 8, 1938.

The president, Dr. James H. Means, Boston, will have charge of the program of general scientific sessions. Dr. James Alexander Miller, New York, the general chairman of the session, will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at headquarters.